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(56) Documents cited
EP 0475206 A2 **US 5149699 A**

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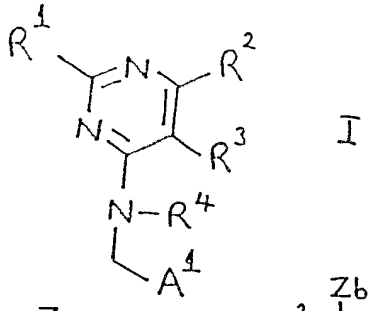
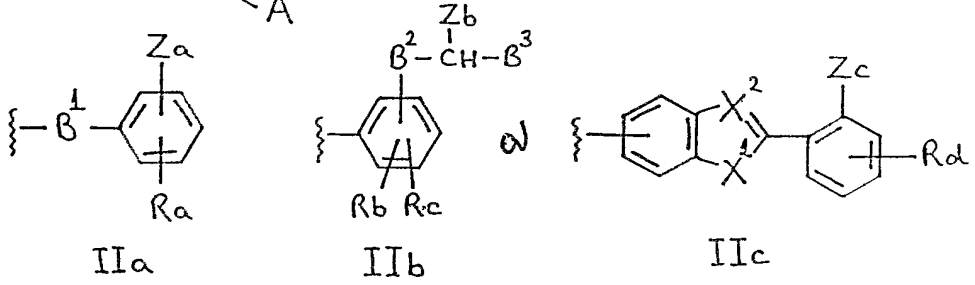
(54) Pyrimidine derivative

(57) Pharmaceutically useful compounds have the formula I, in which R^1, R^2, R^3 and R^4 have the various meanings defined herein, and their non-toxic salts, and pharmaceutical compositions containing them. The compounds are of value in treating conditions such as *hypertension* and *congestive heart failure*. Formula I has the structure:-



I

wherein A' is



IIa IIb IIc

where Za, Zb and Zc are tetrazolyl or represent various defined radical linked by carbonyl or –NH– and the remaining radicals have certain defined meanings.

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HETEROCYCLIC DERIVATIVES

This invention concerns novel heterocyclic derivatives and, more particularly, novel pyrimidine derivatives which possess pharmacologically useful properties in antagonising at least in part one or more of the actions of the substances known as angiotensins, and in particular of that known as angiotensin II (hereinafter referred to as "AII"). The invention also concerns pharmaceutical compositions of the novel compounds for use in treating diseases or medical conditions such as hypertension, congestive heart failure and/or hyperaldosteronism in warm-blooded animals (including man), as well as in other diseases or medical conditions in which the renin-angiotensin-aldosterone system plays a significant causative role. The invention also includes processes for the manufacture of the novel compounds and their use in treating one of the afore-mentioned diseases or medical conditions and for the production of novel pharmaceuticals for use in such medical treatments.

The angiotensins are key mediators of the renin-angiotensin-aldosterone system, which is involved in the control of homeostasis and fluid/electrolyte balance in many warm-blooded animals, including man. The angiotensin known as AII is produced by the action of angiotensin converting enzyme (ACE) on angiotensin I, itself produced by the action of the enzyme renin on the blood plasma protein angiotensinogen. AII is a potent spasmogen especially in the vasculature and is known to increase vascular resistance and blood pressure. In addition, the angiotensins are known to stimulate the release of aldosterone and hence result in vascular congestion and hypertension via sodium and fluid retention mechanisms. Hitherto there have been a number of different approaches to pharmacological intervention in the renin-angiotensin-aldosterone system for therapeutic control of blood pressure and/or fluid/electrolyte balance, including, for example, inhibiting the actions of renin or ACE. However, there remains a continuing need for an alternative approach because of the side-effects and/or idiosyncratic reactions associated with any particular therapeutic approach.

Certain pyrimidines having AII antagonist activity are disclosed in European patent application, publication no. (EPA) 424317, EPA 465323 and International Patent Application, Publication No. WO 91/15209. EPA 475206 and US patent 5149699 (both published after the priority date of the present invention) disclose respectively certain pyrimidines and pyridopyrimidines having AII antagonist activity. In EPA 475206 there is disclosed the compound 4-[N-butyl-N-(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]-2,6-dimethylpyrimidine.

We have now discovered that the compounds of the invention (set out below) surprisingly antagonise one or more of the actions of the substances known as angiotensins (and in particular of AII) and thus minimise the physiological effects associated with their presence in warm-blooded animals (including man) and this is the basis of the invention.

According to the invention there is provided a pyrimidine deivative of the formula I (set out hereinafter, together with the other chemical formulae identified by Roman numerals) wherein
R^1 is hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, phenyl or substituted (1-4C)alkyl, the latter containing one or more fluoro substituents or bearing a (3-8C)cycloalkyl, (1-4C)alkoxy or phenyl substituent;
R^2 is selected from (1-8C)alkyl, (3-8C)cycloalkyl, phenyl or substituted (1-4C)alkyl, the latter containing one or more fluoro substituents or bearing a (3-8C)cycloalkyl, (1-4C)alkoxy or phenyl substituent, halogeno, (1-4C)alkoxy, amino and alkylamino and dialkylamino of up to 6 carbon atoms;
R^3 is selected from hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, substituted (1-4C)alkyl bearing a (3-8C)cycloalkyl, amino, hydroxy, (1-4C)alkoxy, carboxy or (1-4C)alkoxycarbonyl substituent or containing one or more fluoro substituents, hydroxy(1-4C)alkoxy, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, carbamoyl, (1-4C)alkanoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, halogeno, amino, alkylamino and dialkylamino of up to 6 carbon atoms, (1-4C)alkanoylamino, phenyl, phenyl(1-4C)alkyl and benzoyl, the benzene ring of which last three

groups optionally bearing one or two substituents selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl, nitro, hydroxy, carboxy, (1-4C)alkanoylamino, (1-4C)alkanoyl, fluoro(1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, carbamoyl, alkyl or dialkylcarbamoyl of up to 7 carbon atoms, sulphamoyl, N-alkyl or di-(N-alkyl)sulphamoyl of up to 6 carbon atoms, (1-4C)alkoxycarbonyl, (1-4C)alkanesulphonamido, (1-4C)alkyl.$S(O)_n$- [in which n is zero, 1 or 2], 1H-tetrazol-5-yl, phenyl, phenoxy, benzyloxy, benzyloxycarbonyl, benzamido and benzenesulphonamido, the benzene moiety of the last six groups optionally bearing a halogeno, (1-4C)alkyl or (1-4C)alkoxy substituent;

R^4 is hydrogen or (1-4C)alkyl;

or R^2 and R^3 together complete a benzene ring, said benzene ring optionally bearing one or two substituents independently selected from any of the previous values defined for R^3;

or R^2 and R^3 together form an (3-6C)alkenylene group, an (3-6C)alkylene group or an (3-6C)alkylene group in which a methylene is replaced by carbonyl;

or R^3 and R^4 together form a linking group A which is selected from $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CO-CH_2-$, $-CH_2-CO-$, $-CO-CH_2-CH_2-$, $-CH_2-CH_2-CO-$, -CO-CH=CH- and -CH=CH-CO-, and wherein said linking group A optionally bears one or two substituents independently selected from (1-4C)alkyl, substituted (1-4C)alkyl containing one or more fluoro substituents or bearing a (3-8C)cycloalkyl, (1-4C)alkoxy or phenyl substituent, (3-8C)cycloalkyl, (1-4C)alkoxy, halogeno, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, (1-4C)alkanoyl, (1-4C)alkyl.$S(O)_m$- [in which m is zero, 1 or 2] and phenylsulphonyl;

A^1 is a group of the partial formula IIa, IIb or IIc wherein

(1) in partial formula IIa, B^1 is a direct bond or is phenylene optionally bearing a substituent selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano and nitro; Ra is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl or nitro; and Za is 1H-tetrazol-5-yl, a carboxy group or in vivo hydrolysable ester thereof, -CO.NH.(1H-tetrazol-5-yl), or a group of the formula $-CO.NH.CO_2R^8$ in which R^8 is (1-6C)alkyl,

(3-8C)cycloalkyl, trifluoromethyl or phenyl;
(2) in partial formula IIb, B^2 is oxygen, sulphur or a group of the formula $-NR^5-$ in which R^5 is hydrogen or (1-4C)alkyl; Zb has any of the values defined above for Za; B^3 is phenyl optionally bearing one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy and halogeno; and Rb and Rc are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy and halogeno; and
(3) in partial formula IIc, Zc is 1H-tetrazol-5-yl, carboxy or in vivo hydrolysable ester thereof or a group of the formula CF_3SO_2NH-; Rd is selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro; X^1 is oxygen, sulphur or a group of the formula $-NR^6-$ in which R^6 is hydrogen or (1-4C)alkyl; and X^2 is nitrogen or is a group of the formula $-C(R^7)=$ wherein R^7 is hydrogen, (1-4C)alkyl optionally containing one or more fluoro substituents, carbamoyl or N-alkyl or di-(N-alkyl)carbamoyl of up to 7 carbon atoms, halogeno, cyano, (1-4C)alkoxycarbonyl or (1-4C)alkanoyl;

and wherein any of said phenyl moieties of R^1, R^2 or R^8, or of an optional substituent on linking group A, may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano and trifluoromethyl; or a non-toxic salt thereof; but excluding the compound 4-[N-butyl-N-(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]-2,6-dimethylpyrimidine.

It will be appreciated that, depending on the nature of the substituents, certain of the formula I compounds may possess one or more chiral centres and may be isolated in one or more racemic or optically active forms. It is to be understood that this invention concerns any form of such a compound of formula I which possesses the afore-mentioned useful pharmacological properties, it being well known how to make optically active forms, for example by synthesis from suitable chiral intermediates, and how to determine their pharmacological properties, for example by use of the standard tests described hereinafter.

It is to be understood that generic terms such as "alkyl" include both straight and branched chain variants when the carbon

numbers permit. However, when a particular radical such as "propyl" is given, it is specific to the straight chain variant, branched chain variants such as "isopropyl" being specifically named where intended. The same convention applies to other radicals.

A particular value for R^1 or R^2 when it is alkyl is, for example, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl or hexyl; when it is cycloalkyl is, for example, cyclopropyl, cyclopentyl or cyclohexyl; when it is alkyl containing one or more fluoro substitutents is, for example, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl or pentafluoroethyl; and when it is alkyl bearing a cycloalkyl, (1-4C)alkoxy or phenyl substituent is, for example, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopentylethyl, 2-methoxyethyl, 2-ethoxyethyl, benzyl, 1-phenylethyl or 2-phenylethyl.

A particular value for R^2 when it is halogeno is, for example, fluoro, chloro, bromo or iodo; when it is alkoxy is, for example, methoxy, ethoxy; when it is alkylamino or dialkylamino of up to 6 carbon atoms is, for example, methylamino, ethylamino, butylamino, dimethylamino, diethylamino or dipropylamino.

Particular values for R^3 are, by way of example,
for alkyl: methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl or hexyl;
for cycloalkyl: cyclopropyl, cyclopentyl or cyclohexyl;
for alkyl bearing a cycloalkyl, amino, hydroxy, alkoxy, carboxy or alkoxycarbonyl substituent: cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopentylethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, aminomethyl, 2-aminoethyl, methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, 2-methoxycarbonylethyl or 2-ethoxycarbonylethyl;
for alkyl containing one or more fluoro substituents: fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl or pentafluoroethyl;
for hydroxyalkoxy: hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl or 3-hydroxypropyl;

for alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl or propoxycarbonyl;
for alkenyloxycarbonyl: allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl or 3-methyl-3-butenyloxycarbonyl;
for alkanoyl: formyl, acetyl or butyryl;
for N-alkylcarbamoyl: N-methyl or N-ethylcarbamoyl;
for di(N-alkyl)carbamoyl: N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl;
for halogeno: fluoro, chloro, bromo or iodo;
for alkylamino: methylamino, ethylamino or butylamino;
for dialkylamino: dimethylamino, diethylamino or dipropylamino;
for alkanoylamino: formamido, acetamido or propanamido; and
for phenylalkyl: benzyl, 1-phenylethyl or 2-phenylethyl.

A particular value for R^4, R^5 or R^6 when it is alkyl is, for example, methyl, ethyl or propyl.

Particular values for an optional substituent on R^3 when it is phenyl, phenyl(1-4C)alkyl or benzoyl, or for optional substituents on R^2 and R^3 when together they complete a benzene ring, include, by way of example, for alkyl: methyl and ethyl; for alkoxy: methoxy and ethoxy; and for halogeno: chloro, bromo and iodo; for alkanoylamino: formamido, acetamido and propanamido; for alkanoyl: formyl, acetyl and butyryl; for fluoroalkoxy: trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy and 3,3,3-trifluoropropoxy; for hydroxyalkyl: hydroxymethyl, 1-hydroxyethyl and 2-hydroxyethyl; for alkoxyalkyl: 2-methoxyethyl and 2-ethoxyethyl; for N-alkylcarbamoyl: N-methyl and N-ethylcarbamoyl; for di(N-alkyl)carbamoyl: N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl; for N-alkylsulphamoyl: N-methyl and Nethylsulphamoyl; for di(N-alkyl)sulphamoyl: N,N-dimethylsulphamoyl and N,N-diethylsulphamoyl; for alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; for alkanesulphonamido: metanesulphonamido and ethanesulphonamido; for alkylthio: methylthio and ethylthio; for alkylsulphinyl; methylsulphinyl and ethylsulphinyl; for alkylsulphonyl: methylsulphonyl and ethylsulphonyl; and for phenyl, phenoxy, benzyloxy, benzyloxycarbonyl, benzamido and benzenesulphonamido optionally bearing a substituent: phenyl, phenoxy,

benzyloxy, benzyloxycarbonyl, benzamido and benzenesulphonamido optionally bearing a fluoro, chloro, bromo, methyl, ethyl, methoxy or ethoxy substituent.

A particular value for R^2 and R^3 when together they form (3-6C)alkylene is, for example, trimethylene, tetramethylene or pentamethylene; when together they form (3-6C)alkenylene is, for example, 1-propenylene, 2-propenylene, 1-butenylene, 2-butenylene or 3-butenylene; and when together they form (3-6C)alkylene wherein one of the methylene groups is replaced by a carbonyl group is, for example, 1-oxopropylidene, 3-oxopropylidene, 1-oxobutylidene or 4-oxobutylidene.

Particular values for optional substituents on R^3 and R^4 when together they form linking group A is, include, by way of example, for alkyl: methyl and ethyl; for alkyl containing one or more fluoro substitutents: fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and pentafluoroethyl; for alkyl bearing a cycloalkyl, (1-4C)alkoxy or phenyl substituent: cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopentylethyl, 2-methoxyethyl, 2-ethoxyethyl, benzyl, 1-phenylethyl and 2-phenylethyl; for cycloalkyl: cyclopropyl, cyclopentyl and cyclohexyl; for alkoxy: methoxy, ethoxy and propoxy; for halogeno: fluoro, chloro, bromo and iodo; for alkoxycarbonyl: methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl; for alkenyloxycarbonyl: allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl and 3-methyl-3-butenyloxycarbonyl; for alkanoyl: formyl, acetyl and butyryl; for alkylthio: methylthio and ethylthio; for alkylsulphinyl; methylsulphinyl and ethylsulphinyl; and for alkylsulphonyl: methylsulphonyl and ethylsulphonyl.

A particular value for Ra, Rb, Rc, Rd or an optional substituent on B^1 when it is phenylene, or an optional substituent or substituents on B^3, when it is alkyl is, for example, methyl or ethyl; when it is alkoxy is, for example, methoxy or ethoxy; and when it is halogeno is, for example, fluoro, chloro or bromo.

A particular value for an alkanoyl substituent on B^1 when it

is phenylene is, for example, formyl, acetyl or propionyl.

A particular value for Za, Zb, or Zc when it is an in vivo hydrolysable ester is, for example an ester derived from a (1-6C)alkanol such as methanol or ethanol, or phenol, glycerol or the like.

A particular value for R^8 when it is alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl or pentyl; and when it is cycloalkyl is, for example, cyclobutyl, cyclopentyl or cyclohexyl.

A particular value for R^7 includes, by way of example,
for alkyl: methyl and ethyl;
for alkyl containing one or more fluoro substitutents: fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl and pentafluoroethyl;
for N-alkylcarbamoyl: N-methyl and N-ethylcarbamoyl;
for di(N-alkyl)carbamoyl: N,N-dimethylcarbamoyl and N,N-diethylcarbamoyl;
for halogeno: fluoro, chloro, bromo or iodo;
for alkoxycarbonyl: methoxycarbonyl or ethoxycarbonyl; and
for alkanoyl: formyl, acetyl or propionyl.

Particular values for optional substituents which may be present on phenyl moieties of R^1, R^2 or R^8, or on linking group A include, by way of example, for halogeno: fluoro, chloro and bromo; for alkyl: methyl and ethyl; and for alkoxy: methoxy and ethoxy.

A preferred value for R^1 or R^2 is, for example, methyl, ethyl or propyl.

A preferred value for R^3 is, for example, hydrogen, halogeno (especially iodo) or phenyl(1-4C)alkyl.

A preferred value for R^4 is, for example, hydrogen or methyl.

A preferred value for R^2 and R^3 when together they form

alkylene is, for example, trimethylene or tetramethylene.

A preferred value for R^3 and R^4 when together they form linking group A is, for example, -CH=CH-CO-, $-CH_2-CH_2-CH_2-$ or $-CH_2-CH_2-CO-$.

A preferred value for A^1 is, for example, a group of the partial formula IIa.

A preferred value for B^1 is, for example, a p-phenylene group.

A preferred value for Za, Zb or Zc is, for example, carboxy or 1H-tetrazol-5-yl.

An especially preferred value for Za is when it is attached at the ortho position relative to B^1. Za is 1H-tetrazol-5-yl is particularly preferred.

A preferred value for B^2 is, for example, oxygen.

A particularly preferred combination of values is, for example, R^1 and R^2 are both alkyl.

A preferred group of compounds of the formula I comprises those compounds of the formula I wherein A^1 is a group of the partial formula IIa in which Za is 1H-tetrazol-5-yl or carboxy and R^1, R^2, R^3, R^4, Ra and B^1 have any of the values defined above; and the non-toxic salts thereof. Particularly preferred within this group are those compounds wherein Za is a 1H-tetrazol-5-yl group and especially when it is attached at the ortho position relative to B^1.

Particular groups of novel compounds of the invention are, for example, compounds of the formula I wherein:
(1) R^3 is halogeno and R^1, R^2, R^4 and A^1 have any of the values defined above;
(2) R^3 is (1-4C)alkoxycarbonyl and R^1, R^2, R^4 and A^1 have any of the values defined above;

(3) R^3 is benzoyl optionally bearing one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl, nitro, hydroxy, carboxy, (1-4C)alkanoylamino, (1-4C)alkanoyl, fluoro(1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, carbamoyl, alkyl or dialkylcarbamoyl of up to 7 carbon atoms, sulphamoyl, alkyl or dialkylsulphamoyl of up to 6 carbon atoms, (1-4C)alkoxycarbonyl, (1-4C)alkanesulphonamido, (1-4C)alkyl.$S(O)_n$- [in which n is zero, 1 or 2], 1H-tetrazol-5-yl, phenyl, phenoxy, benzyloxy, benzyloxycarbonyl, benzamido and benzenesulphonamido, the benzene moiety of the last six groups optionally bearing a halogeno, (1-4C)alkyl or (1-4C)alkoxy substituent; and R^1, R^2, R^4 and A^1 have any of the values defined above;

(4) R^3 is phenyl optionally bearing one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl, nitro, hydroxy, carboxy, (1-4C)alkanoylamino, (1-4C)alkanoyl, fluoro(1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, carbamoyl, alkyl or dialkylcarbamoyl of up to 7 carbon atoms, sulphamoyl, alkyl or dialkylsulphamoyl of up to 6 carbon atoms, (1-4C)alkoxycarbonyl, (1-4C)alkanesulphonamido, (1-4C)alkyl.$S(O)_n$- [in which n is zero, 1 or 2], 1H-tetrazol-5-yl, phenyl, phenoxy, benzyloxy, benzyloxycarbonyl, benzamido and benzenesulphonamido, the benzene moiety of the last six groups optionally bearing a halogeno, (1-4C)alkyl or (1-4C)alkoxy substituent; and R^1, R^2, R^4 and A^1 have any of the values defined above;

(5) R^2 and R^3 together form an (3-6C)alkylene group; and R^1, R^4 and A^1 have any of the values defined above; or

(6) R^3 and R^4 together form a linking group A as defined above; and R^1, R^2 and A^1 have any of the values defined above.

Further particular groups of novel compounds of the invention are, for example, compounds of the formula I wherein;

(7) R^3 is phenyl(1-4C)alkyl optionally bearing one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl, nitro, hydroxy, carboxy, (1-4C)alkanoylamino, (1-4C)alkanoyl, fluoro(1-4C)alkoxy, hydroxy(1-4C)alkyl,

(1-4C)alkoxy(1-4C)alkyl, carbamoyl, alkyl or dialkylcarbamoyl of up to 7 carbon atoms, sulphamoyl, alkyl or dialkylsulphamoyl of up to 6 carbon atoms, (1-4C)alkoxycarbonyl, (1-4C)alkanesulphonamido, (1-4C)alkyl.$S(O)_n$- [in which n is zero, 1 or 2], 1H-tetrazol-5-yl, phenyl, phenoxy, benzyloxy, benzyloxycarbonyl, benzamido and benzenesulphonamido, the benzene moiety of the last six groups optionally bearing a halogeno, (1-4C)alkyl or (1-4C)alkoxy substituent; and R^1, R^2, R^4 and A^1 have any of the values defined above; or

(8) R^3 and R^4 together form a linking group $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$ (of which the latter is of particular interest); and R^1, R^2 and A^1 have any of the values defined above.

Compounds of the invention which are of particular interest include, for example, the specific embodiments set out hereinafter in the accompanying Examples, in particular the compounds of examples 1, 3, 4, 6, 7, 8, 9 and 10. These compounds, or a non-toxic salt thereof, are provided as a further feature of the invention.

Although all of the formula I compounds can form salts with suitable acids, it will be appreciated that those compounds of formula I wherein Za, Zb or Zc is other than an ester group or in which R^3 or linking group A bears a carboxy group can form salts with bases as well as with acids. Particularly suitable non-toxic salts for such compounds therefore also include, for example, salts with bases affording physiologically acceptable cations, for example, alkali metal (such as sodium and potassium), alkaline earth metal (such as magnesium and calcium), aluminium and ammonium salts, as well as salts with suitable organic bases, such as with ethanolamine, methylamine, diethylamine or triethylamine, as well as salts with acids forming physiologically acceptable anions, such as salts with mineral acids, for example with hydrogen halides (such as hydrogen chloride and hydrogen bromide), sulphuric and phosphoric acid, and with strong organic acids, for example with p-toluenesulphonic and methanesulphonic acids.

The compounds of formula I may be obtained by standard

procedures of organic chemistry well known in the art for the production of structurally analogous compounds. Such procedures are provided as a further feature of the invention and include, by way of example, the following procedures in which the generic radicals have any of the values given above, unless stated otherwise:

a) For those compounds in which A^1 is a group of the partial formula IIa, IIb or IIc in which Za, Zb and Zc respectively are carboxy, a carboxylic acid derivative of the formula IIIa, IIIb or IIIc in which Qa, Qb and Qc respectively are protected carboxy groups selected from (1-6C)alkoxycarbonyl (especially methoxy-, ethoxy-, propoxy- or t-butoxy-carbonyl), phenoxycarbonyl, benzyloxycarbonyl and carbamoyl, is converted to carboxy.

The conversion may be carried out, for example by hydrolysis, conveniently in the presence of a suitable base such as an alkali metal hydroxide, for example, lithium, sodium or potassium hydroxide. The hydrolysis is generally carried out in the presence of a suitable aqueous solvent or diluent, for example in an aqueous (1-4C)alkanol, such as aqueous methanol or ethanol. However, it may also be performed in a mixture of an aqueous and non-aqueous solvent such as water and toluene using a conventional quaternary ammonium phase transfer catalyst. The hydrolysis is generally performed at a temperature in the range, for example, 0 - 120°C, depending on the reactivity of the group Qa, Qb or Qc. In general, when Qa, Qb or Qc is carbamoyl, temperatures in the range, for example, 40 - 120°C are required to effect the hydrolysis.

Alternatively, when Qa, Qb or Qc is benzyloxycarbonyl the conversion may also be performed by hydrogenolysis, for example using hydrogen at 1-3 bar in the presence of a suitable catalyst, such as palladium on charcoal or on calcium sulphate, in a suitable solvent or diluent such as a (1-4C)alkanol (typically ethanol or 2-propanol) and at a temperature in the range, for example, 0 - 40°C.

Further, when Qa, Qb or Qc is t-butoxycarbonyl, the conversion may also be carried out by hydrolysis at a temperature in

the range, for example, 0 - 100°C, in the presence of a strong acid catalyst, such as trifluoroacetic acid. The hydrolysis may either be performed in an excess of the acid or in the presence of a suitable diluent such as tetrahydrofuran, t-butyl methyl ether or 1,2-dimethoxyethane.

b) For those compounds of formula I in which A^1 is a group of the partial formula IIa, IIb or IIc in which Za, Zb and Zc respectively are tetrazolyl, a compound of the formula IVa, IVb or IVc in which La, Lb and Lc respectively are suitable protecting groups, such as trityl, benzhydryl, trialkyltin (for example trimethyltin or tributyltin) or triphenyltin affixed to a nitrogen of the tetrazolyl moiety, is deprotected.

The reaction conditions used to carry out the deprotection necessarily depend on the nature of the group La, Lb or Lc. As an illustration, when it is trityl, benzhydryl, trialkyltin or triphenyltin, the decomposition conditions include, for example, acid catalysed hydrolysis in a mineral acid (such as aqueous hydrochloric acid), conveniently in an aqueous solvent (such as aqueous dioxan or 2-propanol). Alternatively, a trityl or benzhydryl group may be removed by hydrogenolysis, for example as described in (a) above for conversion of a benzyloxycarbonyl to a carboxy.

Compounds of the formula IVa, IVb or IVc wherein La, Lb and Lc respectively are trialkyltin or triphenyltin may be obtained, for example, by reaction of a nitrile of the formula IXa, IXb or IXc respectively with a trialkyltin azide, such as tributyltin azide, or triphenyltin azide respectively. The reaction is conveniently carried out in a suitable solvent or diluent, such as toluene or xylene, and at a temperature in the range, for example, 50-150°C. Nitriles of the formula IXa, IXb or IXc may be obtained, for example, by alkylation of a 4-aminopyrimidine of the formula V wherein R^1 and R2 are other than hydrogen with a nitrile of the formula Xa, Xb or Xc respectively wherein Hal. stands for a suitable leaving group such as chloro, bromo, iodo, methanesulphonyloxy or p-toluenesulphonyloxy, using similar conditions to those used in process (c) described hereinafter.

The necessary compounds of formula Xa, Xb or Xc, as well as those of formula VIIa, VIIb, VIIc, VIIIa, VIIIb or VIIIc described herein, may be obtained, for example, as described in European patent application, publication nos. 253310, 291969, 453210, 434249, 430709, 429257 and International patent application no. WO 91/11999.

The nitriles of the formula IXa, IXb or IXc may also be obtained, for example, by reaction of a pyrimidine of the formula VI wherein Y^1 is a suitable leaving group (such as chloro, bromo, iodo, methanesulphonyl, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy) with an amine of the formula XIa, XIb or XIc respectively, using similar conditions to those used in process (d) described hereinafter.

The amines of the formula XIa, XIb or XIc may be obtained, for example, by standard procedures such as from the corresponding compounds of formula Xa, Xb or Xc by reaction with the appropriate amine of formula R^4NH_2 using conventional conditions.

Alternatively, compounds of the formula IVa, IVb or IVc may be obtained, for example, by reaction of a pyrimidine of the formula VI wherein Y^1 is as defined above with an amine of the formula XIIa, XIIb or XIIc respectively under similar conditions to those described in process (d) hereinafter. The amines of formula XIIa, XIIb or XIIc may be obtained, for example, from the corresponding compound of formula VIIIa, VIIIb or VIIIc respectively by reaction with the appropriate amine of formula R^4NH_2 using standard conditions.

c) For compounds of the formula I, an aminopyrimidine of the formula V is alkylated with a compound of the formula VIIa, VIIb or VIIc wherein Hal. stands for a suitable leaving group such as chloro, bromo, iodo, methanesulphonyloxy or p-toluenesulphonyloxy.

The reaction is preferably carried out in the presence of a suitable non-nucleophillic base, for example, an alkali metal tert-butoxide such as sodium or potassium tert-butoxide, an alkali metal hydride such as sodium hydride, or an alkali metal carbonate

such as sodium or potassium carbonate, or an organic base such as diisopropylethylamine or 4-dimethylaminopyridine. The reaction is conveniently carried out in a suitable solvent or diluent, for example, a (1-4C)alkanol such as methanol or ethanol, or in a polar solvent such as N,N-dimethylformamide or N-methylpyrrolidone and at a temperature in the range, for example, 10 - 100°C. In carrying out process (c), when in the starting material Za, Zb or Zc is an acidic group about two molecular equivalents of a suitable base is generally required, whereas when Za, Zb or Zc does not bear an acidic group the presence of one molecular equivalent of a suitable base is generally sufficient.

Procedure (c) is particularly suitable for the production of those compounds of the formula I in which Za, Zb or Zc is an ester group, for example wherein Za, Zb or Zc is an (1-6C)alkyl, benzyl or phenyl ester, which compounds are also starting materials of formula IIIa, IIIb and IIIc respectively for the reactions described in (a) above. Similarly, using an analogous procedure, but starting with the appropriate compound of the formula VIIIa, VIIIb or VIIIc, the starting materials of formula IVa, IVb or IVc respectively may be obtained for procedure (b).

Many of the aminopyrimidines of formula V are already known and the remainder can be made by analogy therewith using standard procedures of organic chemistry well known in the art, for example as described in standard works of heterocyclic chemistry such as "Chemistry of Heterocyclic Compounds" edited by Weissberger, or as illustrated in Scheme 1.

(d) For compounds of formula I, a heterocyclic derivative of the formula VI wherein Y^1 is a suitable leaving group (such as chloro, bromo, iodo, methanesulphonyl, methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy) is reacted with an amine of the formula XIIIa, XIIIb or XIIIc.

The reaction is optionally carried out in the presence of a suitable base, for example an alkali metal carbonate or bicarbonate

such as sodium or potassium carbonate or bicarbonate, or an organic base for example a tertiary amine such as triethylamine. The reaction is conveniently carried out in a suitable solvent or diluent, for example a (1-4C)alkanol such as methanol, ethanol or butanol, a non-polar solvent such as dioxane or diphenyl ether, or a polar solvent such as N,N-dimethylformamide or N-methylpyrrolidone, and usually at a temperature in the range of 40 to 180°C.

Heterocyclic derivatives of the formula VI wherein Y^1 is halogeno may be obtained, for example, by halogenation of the corresponding 4-pyrimidones, themselves already known or which can be made by analogy therewith using procedures well known in the art and described in standard works of organic chemistry such as "Chemistry of Heterocyclic Compounds" edited by Weissberger. For example, the formula VI compounds may be obtained by reaction of the corresponding 4-pyrimidone with phosphorus oxychloride in the absence of a solvent, or in the presence of an inert solvent or diluent such as toluene or dioxane, and at a temperature in the range 60 - 110°C. Compounds of the formula VII wherein Y^1 is methanesulphonyloxy, p-toluenesulphonyloxy or trifluoromethanesulphonyloxy and R^1 and R^3 are other than hydrogen may be obtained, for example, by acylation of the corresponding 4-pyrimidone with the corresponding sulphonyl chloride under standard conditions. Compounds of the formula VI wherein Y^1 is methanesulphonyl may be obtained from alkylation of the corresponding mercaptopyrimidine, themselves known or obtained by analogy therewith, followed by oxidation under standard conditions. The amines of formula XIIIa, XIIIb and XIIIc may be obtained, for example, from the corresponding compound of formula VIIa, VIIb and VIIc respectively by reaction with the appropriate amine of formula R^4NH_2 using standard conditions

(e) For those compounds of formula I wherein A^1 is a group of partial structure IIc in which Zc is a group of the formula CF_3SO_2NH-, a compound of formula XIV is reacted with trifluoromethanesulphonic acid anhydride.

The reaction is preferably carried out in the presence of a

base, such as triethylamine, and conveniently in a suitable solvent or diluent, for example dichloromethane, and at a temperature in the range of -78°C to ambient temperature. The compounds of the formula XIV may be obtained by alkylation of a compound of formula V with a compound of the formula XV (itself obtained using analogous procedures to those described in EPA 429257 and 430709) using similar conditions to those of process (c) above, followed by reduction of the nitro group in the intermediate obtained, for example by conventional catalytic hydrogenation.

Whereafter, those compounds of formula I wherein Za, Zb or Zc is 1H-tetrazol-5-yl may be obtained by stepwise conversion of a compound of the formula I wherein Za, Zb or Zc is a carboxylic acid or ester group respectively into the corresponding nitrile under standard conditions, followed by reaction of the nitrile with an azide such as an alkali metal azide, preferably in the presence of an ammonium halide, and preferably in the presence of a suitable polar solvent such as N,N-dimethylformamide and at a temperature in the range, for example, 50 to 160°C.

Whereafter, those compounds of the formula I wherein Za, Zb or Zc is -CO.NH.(1H-tetrazol-5-yl), a group of the formula $-CO.NH.SO_2R^8$ or an ester group, may be obtained, for example, by reacting a carboxylic acid of the formula I in which Za, Zb and Zc is carboxy (or a reactive derivative of said acid) with 5-aminotetrazole, a sulphonamide of the formula $NH_2.SO_2R^8$ or a salt thereof (for example, an alkali metal salt), or an appropriate alcohol or with a salt thereof (for example, an alkali metal thereof). Suitable reactive derivatives include, for example the chloride, bromide, azide, anhydride and mixed anhydride with formic or acetic acid of the carboxylic acid of formula I as defined above. When the free acid form is used, the reaction is generally carried out in the presence of a suitable dehydrating agent such as dicyclohexycarbodiimide or 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide in the presence of a base such as triethylamine or pyridine. When a reactive derivative is used, either the reaction is carried out in the presence of a base such as mentioned above, or, for the preparation of a compound of the

formula I wherein Za, Zb or Zc is a group of the formula $-CO.NH.SO_2R^8$ or an ester group, the sulphonamide or hydroxy compound is used in the form of a salt, such as its alkali metal salt (in particular the lithium, sodium or potassium salt thereof). The reaction is generally performed in the presence of a suitable diluent or solvent such as dioxan, t-butyl methyl ether or tetrahydrofuran and at a temperature in the range, for example, 0 - 60°C.

Whereafter, when a non-toxic salt of a compound of formula I is required, it may be obtained, for example, by reaction with the appropriate base affording a physiologically acceptable cation, or with the appropriate acid affording a physiologically acceptable anion, or by any other conventional salt formation procedure.

Further, when an optically active form of a compound of formula I is required, one of the aforesaid processes may be carried out using an optically active starting material. Alternatively, the racemic form of a compound of formula I in which Za, Zb or Zc is an acidic group may be resolved, for example by reaction with an optically active form of a suitable organic base, for example, ephedrine, N,N,N-trimethyl(1-phenylethyl)ammonium hydroxide or 1-phenylethylamine, followed by conventional separation of the diastereoisomeric mixture of salts thus obtained, for example by fractional crystallisation from a suitable solvent, for example a (1-4C)alkanol, whereafter the optically active form of said compound of formula I may be liberated by treatment with acid using a conventional procedure, for example using an aqueous mineral acid such as dilute hydrochloric acid.

According to a further aspect of the invention, there is provided a process for the manufacture of a compound of the formula I wherein A^1 is a group of partial structure IIa in which Za is tetrazolyl, B^1 is p-phenylene optionally bearing a substituent selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano and nitro and R^1, R^2, R^3, R^4, and Ra have any of the meanings defined hereinbefore; which comprises reaction of a compound of the formula XVI wherein P^1 is an electron-deficient phenyl

group or a pyrimidyl or pyridyl group; Re is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano or nitro; and R^1, R^2, R^3, R^4 and Ra have any of the values defined above; with a base selected from an alkali metal hydroxide, (1-12C)alkanolate, (1-12C)alkanethiolate, phenolate, thiophenolate or diphenylphosphide, wherein any phenyl ring of the latter three groups may optionally bear a (1-4C)alkyl, (1-4C)alkoxy or halogeno group.

A particular value for P^1 includes, for example, a phenyl group bearing 1, 2 or 3 electron-withdrawing groups independently selected from nitro, cyano and trifluoromethyl.

A particular value for Re when it is alkyl is, for example, methyl or ethyl; when it is alkoxy is, for example, methoxy or ethoxy; and when it is halogeno is, for example, fluoro, chloro, bromo or iodo.

A particular value for a base includes the following by way of example:-
for an alkali metal hydroxide: sodium or potassium hydroxide;
for an alkali metal alkanolate: an alkali metal (1-8C)alkanolate, for example an alkali metal (1-4C)alkoxide, such as sodium or potassium methoxide, ethoxide, propoxide or butoxide;
for an alkali metal alkanethiolate: an alkali metal (1-8C)alkanethiolate, for example an alkali metal (1-4C)alkanethiolate such as sodium or potassium methanethiolate, ethanethiolate, propanethiolate or butanethiolate.

A particular value for an optional substituent on a phenyl group of an alkali metal phenolate, thiophenolate or diphenylphosphide, when it is alkyl is, for example, methyl or ethyl; when it is alkoxy is, for example, methoxy or ethoxy; and when it is halogeno is, for example, fluoro, chloro or bromo.

A preferred value for P^1 is, for example, a nitrophenyl group, especially 4-nitrophenyl.

A preferred value for X is, for example, when it is unsubstituted p-phenylene.

A particularly preferred base is an alkali metal alkanethiolate such as sodium or potassium propanethiolate, an alkali metal alkanolate such as sodium or potassium ethoxide, or an alkali metal thiophenolate such as sodium or potassium 4-fluorothiophenolate.

It will be appreciated that when the base is an alkali metal alkanolate, alkanethiolate, phenolate, thiophenolate or diphenylphosphide, it may be generated in situ from the corresponding alkanol, alkanethiol, phenol, thiophenol or diphenylphosphine with a suitable alkali metal base such as an alkali metal hydride, for example, lithium, potassium or sodium hydride.

The process of the invention is particularly useful for the preparation of compounds of the formula I wherein the tetrazolyl group is at the ortho position relative to the adjacent phenyl group.

The reaction is conveniently carried out in a suitable inert organic solvent or diluent, for example, a polar solvent such as N,N-dimethylformamide or N-methylpyrrolidone. Alternatively, an alkanol such as methanol or ethanol may be used, for example, when an alkali metal hydroxide or alkoxide such as sodium or potassium hydroxide, methoxide or ethoxide is employed. The reaction is generally carried out at a temperature in the range, for example, -30°C to 50°C. It will be appreciated that the choice of temperature will depend on the nature of the base employed. For example, when an alkali metal alkanethiolate or alkanolate is used, a temperature in the range of 0°C to ambient temperature is preferred.

Compounds of the formula XVI may be obtained by reaction of a boronic acid of the formula XVII with a compound of the formula XVIII wherein P^1 is an electron-deficient phenyl group or a pyrimidyl or pyridyl group having any of the meanings defined above and W is a bromo, iodo or trifluoromethanesulphonyloxy group, in the presence of a palladium(0) or palladium (II) catalyst, such as

tetrakis(triphenylphosphine)palladium (0) or palladium (II)chloride. The reaction is preferably carried out in the presence of a base, such as sodium or potassium carbonate, in an inert solvent or diluent, for example, a hydrocarbon such as toluene or xylene, an ether, such as dioxan or tetrahydrofuran, an (1-4C)alkanol such as methanol or ethanol, water, or mixture thereof, for example a mixture of water, methanol and toluene, and at a temperature in the range of, for example, 50°C to 150°C., and conveniently at or about the reflux temperature of the solvent or mixture of solvents used.

Compounds of the formula XVII may be obtained, for example, by heating at reflux a 4-methylphenylboronic acid in a solvent such as methyl chloroform with azeotropic removal of water, followed by radical bromination of the product which may be carried out in situ, for example with bromine or N-bromosuccinimide in the presence of azo(bisisobutyronitrile). The resultant 4-bromomethylphenylboronic acid anhydride may then be used to alkylate a compound of the formula V (using similar alkylation conditions to those used in process (c) described above), followed by subsequent acidic hydrolysis, to give a formula XVII compound. Alternatively the product from the alkylation step prior to hydrolysis may be isolated and reacted directly with a compound of the formula XVIII under similar conditions to those described above to obtain a formula XVI compound directly. In a yet further alternative procedure, a 4-methylphenylboronic acid and an appropriate alkanediol, for example 2,2-dimethylpropan-1,3-diol, may be heated at reflux in a solvent (such as cyclohexane) with azeotropic removal of water followed by free radical bromination of the product, which may be carried out in situ. The resultant bromomethyl compound may then be reacted using analogous procedures to those described above for the 4-bromomethylphenylboronic acid anhydride to obtain a formula XVII compound or a compound of the formula XVI directly. Compounds of the formula XVIII may be obtained, for example, by reaction of an appropriately substituted benzoyl chloride with an amine of formula $P^1.NH_2$ under standard conditions. The resultant amide is then, for example, reacted with thionyl chloride in the presence of triethylamine and N,N-dimethylformamide in acetonitrile at ambient temperature to form the corresponding imidoyl chloride, which

is reacted in situ with triethylamine, sodium azide and tetrabutylammonium bromide at 10-30°C to give the formula XVIII compound.

Whereafter, the optional subsequent steps of non-toxic salt formation and/or formation of an optically active form of a compound of the formula I, may be carried out as described above for procedures (a) to (e).

Certain of the intermediates defined herein are novel, for example the compounds of the formula IIIa, IIIb, IIIc, IVa, IVb, IVc, IXa, IXb and IXc, and are provided as a further feature of the invention.

As stated above, the compounds of formula I will have beneficial pharmacological effects in warm-blooded animals (including man) in diseases and medical conditions where amelioration of the vasoconstrictor and fluid retaining properties of the renin-angiotensin-aldosterone system is desirable, at least in part by antagonism of one or more of the physiological actions of AII. The compounds of the invention will thus be useful in the treatment of diseases or medical conditions such as hypertension, congestive heart failure and/or hyperaldosteronism in warm-blooded animals (including man), as well as in other diseases or medical conditions in which the renin-angiotensin-aldosterone system plays a significant causative role. The compounds of the invention may also be useful for the treatment of ocular hypertension, glaucoma, cognitive disorders (such as Alzheimer's disease, amnesia, senile dementia and learning disorders), as well as other diseases such as renal failure, cardiac insufficiency, post-myocardial infarction, cerebrovascular disorders, anxiety, depression and certain mental illnesses such as schizophrenia.

The antagonism of one or more of the physiological actions of AII and, in particular, the antagonism of the interaction of AII with the receptors which mediate its effects on a target tissue, may be assessed using one or more of the following, routine laboratory

procedures:

Test A: This in vitro procedure involves the incubation of the test compound initially at a concentration of 100 micromolar (or less) in a buffered mixture containing fixed concentrations of radiolabelled AII and a cell surface membrane fraction prepared from a suitable angiotensin target tissue. In this test, the source of cell surface membranes is the guinea pig adrenal gland which is well known to respond to AII. Interaction of the radiolabelled AII with its receptors (assessed as radiolabel bound to the particulate membrane fraction following removal of unbound radiolabel by a rapid filtration procedure such as is standard in such studies) is antagonized by compounds which also bind to the membrane receptor sites and the degree of antagonism (observed in the test as displacement of membrane-bound radioactivity) is determined readily by comparing the receptor-bound radioactivity in the presence of the test compound at the specified test concentration with a control value determined in the absence of the test compound. Using this procedure compounds showing at least 50% displacement of radiolabelled AII binding at a concentration of 10^{-4} M are retested at lower concentrations to determine their potency. For determination of the IC_{50} (concentration for 50% displacement of radiolabelled AII binding), concentrations of the test compound are ordinarily chosen to allow testing over at least four orders of magnitude centred about the predicted approximate IC_{50}, which latter is subsequently determined from a plot of percentage displacement against concentration of the test compound.

In general, acidic compounds of formula I as defined above show significant inhibition in Test A at a concentration of 50 micromolar or much less.

Test B: This in vitro test involves the measurement of the antagonistic effects of the test compound against AII-induced contractions of isolated rabbit aorta, maintained in a physiological salt solution at 37°C. In order to ensure that the effect of the compound is specific to antagonism of AII, the effect of the test compound on noradrenaline-induced contractions may also be determined

in the same preparation.

In general, acidic compounds of formula I as defined above show significant inhibition in **Test B** at a final concentration of 50 micromolar or much less. [Note: Compounds of formula I wherein Za, Zb or Zc is an ester group in general show only weak activity in the in vitro **Tests A or B.**]

Test C: This in vivo test involves using terminally-anaesthetised or conscious rats in which an arterial catheter has been implanted under anaesthesia for the measurement of changes in blood pressure. The AII antagonistic effects of the test compound following oral or parenteral administration, are assessed against angiotensin II-induced pressor responses. To ensure that the effect is specific, the effect of the test compound on vasopressin-induced pressor responses may also be determined in the same preparation.

The compounds of formula I generally show specific AII-antagonist properties in **Test C** at a dose of 50 mg/kg body weight or much less, without any overt toxicological or other untoward pharmacological effect.

Test D: This in vivo test involves the stimulation of endogenous AII biosynthesis in a variety of species including rat, marmoset and dog by introducing a diet of low sodium content and giving appropriate daily doses of a saluretic known as frusemide. The test compound is then administered orally or parenterally to the animal in which an arterial catheter has been implanted under anaesthesia for the measurement of changes in blood pressure.

In general compounds of formula I will show AII-antagonist properties in **Test D** as demonstrated by a significant reduction in blood pressure at a dose of 50 mg/kg body weight or much less, without any overt toxicological or other untoward pharmacological effect.

The compounds of formula I will generally be administered for therapeutic or prophylactic purposes to warm-blooded animals

(including man) requiring such treatment in the form of a pharmaceutical composition, as is well known in the pharmaceutical art. According to a further feature of the invention there is provided a pharmaceutical composition comprising a compound of formula I, or a salt as defined above, together with a pharmaceutically acceptable diluent or carrier. Such compositions will conveniently be in a form suitable for oral administration (e.g. as a tablet, capsule, solution, suspension or emulsion) or parenteral administration (e.g. as an injectable aqueous or oily solution, or injectable emulsion).

The compounds of formula I, or a non-toxic salt thereof, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as a beta-adrenergic blocker (for example atenolol), a calcium channel blocker (for example nifedipine), an angiotensin converting enzyme (ACE) inhibitor (for example lisinopril) or a diuretic (for example furosemide or hydrochlorothiazide). It is to be understood that such combination therapy constitutes a further aspect of the present invention.

In general a compound of formula I (or a pharmaceutically acceptable salt thereof as appropriate) will generally be administered to man so that, for example, a daily oral dose of up to 50 mg/kg body weight (and preferably of up to 10 mg/kg) or a daily parenteral dose of up to 5 mg/kg body weight (and preferably of up to 1 mg/kg) is received, given in divided doses as necessary, the precise amount of compound (or salt) administered and the route and form of administration depending on size, age and sex of the person being treated and on the particular disease or medical condition being treated according to principles well known in the medical arts.

In addition to their aforesaid use in therapeutic medicine in humans, the compounds of formula I are also useful in the veterinary treatment of similar conditions affecting commercially valuable warm-blooded animals, such as dogs, cats, horses and cattle. In general for such treatment, the compounds of the formula I will

generally be administered in an analogous amount and manner to those described above for administration to humans. The compounds of formula I are also of value as pharmacological tools in the development and standardisation of test systems for the evaluation of the effects of AII in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the continuing search for new and improved therapeutic agents.

The invention will now be illustrated by the following non-limiting Examples in which, unless otherwise stated:-

(i) concentrations and evaporations were carried out by rotary evaporation in vacuo;

(ii) operations were carried out at room temperature, that is in the range 18-26°C;

(iii) flash column chromatography was performed on Merck Kieselgel 60 (Art. no. 9385) obtained from E Merck, Darmstadt, Germany;

(iv) yields, where given, are intended for the assistance of the reader only and are not necessarily the maximum attainable by diligent process development;

(v) ^{1}H NMR spectra were normally determined at 200 MHz in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; m, multiplet; t, triplet; br, broad; d,doublet;

(vi) ^{13}C NMR spectra were normally determined at 100 MHz in $CDCl_3$ or d_6-dimethylsulphoxide (d_6-DMSO) using the solvent signal as internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS; and

(vii) all end-products had satisfactory microanalyses.

EXAMPLE 1

Concentrated hydrochloric acid (0.5 ml) was added to a solution of 2,6-dimethyl-4-[N-(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]pyrimidine (A) (0.5 g) in methanol and the mixture was stirred for 10 minutes. Volatile material was removed by evaporation and the residue was purified by crystallisation from iso-propanol/ethanol to give **2,6-dimethyl-4-[N-(2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl)amino]pyrimidine** hydrochloride (138 mg), as an off white solid, m.p. 248-252°C (decomposition); NMR (d_6-DMSO): 2.37(s, 3H), 2.52(s, 3H), 4.63(d, 2H), 6.54(s, 1H), 7.11(d, 2H), 7.25(d, 2H), 7.43-7.66(m, 4H), 9.29(broad s, 1H); mass spectrum (positive fast atom bombardment (+ve FAB), DMSO/methanol/nitrobenzyl alcohol): $358(M+H)^+$; microanalysis, found: C, 60.1; H, 5.3; N, 23.4%; $C_{20}H_{19}N_7.HCl.0.25C_2H_5OH.0.25H_2O$ requires: C, 60.0; H, 5.4; N, 23.2%.

The starting material A was prepared as follows:

(i) 4-Amino-2,6-dimethylpyrimidine (B) (2.5 g) was added to a suspension of sodium hydride (60% dispersion in mineral oil; 1.11 g) in N,N-dimethylformamide (DMF) (180 ml) and the mixture was stirred for 6 hours. 5-[2-(4'-Bromomethylbiphenyl)]-2-triphenylmethyl-2H-tetrazole (14.8 g) (obtained as described in European patent application, publication no. 291969) was added and the mixture was stirred for 16 hours. Solvent was removed by evaporation and the residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with saturated sodium chloride solution and dried. Solvent was removed by evaporation and the residue was purified by flash chromatography eluting with ethyl acetate/methanol (49:1 v/v). Fractions containing the desired compound were combined and solvent was removed by evaporation. The residue was further purified by flash chromatography eluting with dichloromethane/methanol (19:1 v/v) to give 2,6-dimethyl-4-[N-(2'-(1H-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]pyrimidine (A) (1.52 g), as a white foam; NMR ($CDCl_3$): 2.26(s, 3H), 2.50(s, 3H), 4.41(d, 2H), 4.88(broad s, 1H), 5.90(s, 1H), 6.86-6.97(m, 6H), 7.02-7.17(m, 4H), 7.19-7.55(complex m, 12H), 7.96(m, 1H); mass spectrum (+ve FAB, methanol/nitrobenzyl alcohol): $600(M+H)^+$.

EXAMPLES 2-7

Using an analogous procedure to that described in Example 1, but starting from the appropriate compound of formula IVa wherein La is triphenylmethyl, the following compounds of formula I (in which A^1 is a group of partial structure IIa) were obtained in yields of 52-92%.

(Example 2): **2,6-dimethyl-4-[N-methyl-N-(2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl)amino]pyrimidine** hydrochloride as a solid, m.p. 222-226°C; NMR (d_6-DMSO/d_4-acetic acid): 2.41,2.46(d of s, 3H), 2.56,2.58(d of s, 3H), 3.17,3.32(d of s, 3H), 4.85,5.05(d of s, 2H), 6.75,6.9(d of s, 1H), 7.05-7.4(complex m, 4H), 7.45-7.8(complex m, 4H); mass spectrum (+ve FAB, glycerol/methanol): 372$(M+H)^+$; microanalysis, found: C, 61.3; H, 5.2; N, 26.6%; $C_{21}H_{21}N_7$.HCl requires C, 61.8; H, 5.44; N, 24.0%.

(Example 3): **2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)-amino]-5,6,7,8-tetrahydroquinazoline** hydrochloride as a solid, m.p. 277-278°C; NMR (d_6-DMSO): 1.19(t, 3H), 1.78(m, 4H), 2.38(m, 2H), 2.67(m, 2H), 2.74(q, 2H), 4.70(d, 2H), 7.06(d, 2H), 7.27(d, 2H), 7.56(m, 4H), 9.05(t, 1H); mass spectrum (+ve FAB methanol/nitrobenzyl alcohol): 412$(M+H)^+$; microanalysis, found: C, 64.1; H, 5.9; N, 21.8%; $C_{24}H_{25}N_7$.HCl requires: C, 64.3; H, 5.8; N, 21.9%.

(Example 4): **2,6-dimethyl-5-iodo-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]pyrimidine** hydrochloride as a solid, m.p. 221-223°C; NMR (d_6-DMSO): 2.40(s, 3H), 2.50(s, 3H), 4.72(d, 2H), 7.06(d, 2H), 7.25(d, 2H), 7.64(m, 4H), 8.92(broad t, 1H); mass spectrum (+ve FAB, DMSO/glycerol): 484$(M+H)^+$; microanalysis, found: C, 45.8; H, 3.7; N, 18.6%; $C_{20}H_{18}IN_7$.HCl requires: C, 46.2; H, 3.7; N, 18.9%.

(Example 5): **2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)-amino]quinazoline** hydrochloride as a solid, m.p. 256-257°C; NMR (d_6-DMSO): 1.31(t, 3H), 2.93(q, 2H), 4.95(d, 2H), 7.07(d, 2H), 7.37(d, 2H), 7.60(m, 5H), 7.88(d, 1H), 8.00(m, 1H), 8.59(d, 1H), 10.83(t, 1H); mass spectrum (+ve FAB, DMSO/methanol/nitrobenzyl

alcohol): 408$(M+H)^+$; microanalysis, found: C, 64.3; H, 5.0; N, 21.6%; $C_{24}H_{21}N_7.HCl.0.25CH_3OH$ requires: C, 64.4; H, 5.1; N, 21.7%.

(Example 6): **2,6-diethyl-5-iodo-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]pyrimidine** hydrochloride as a solid m.p. 226-229°C; NMR (d_6-DMSO): 1.18(d of t, 6H), 2.80(d of q, 4H), 4.7(d, 2H), 7.05(d, 2H), 7.27(d, 2H), 7.85(m, 4H), 8.9(broad s, 1H); mass spectrum (+ve FAB, DMSO/nitrobenzyl alcohol): 512$(M+H)^+$; microanalysis, found: C, 48.6; H, 4.2; N, 17.8%; $C_{22}H_{22}IN_7.HCl$ requires: C, 48.2; H, 4.2; N, 17.9%.

(Example 7): **2,4-diethyl-8-[(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)]pyrido[2,3-d]pyrimidin-7(8H)-one** as a solid, m.p. 214-215°C; NMR (d_6-DMSO): 1.26(d of t, 6H), 2.89(q, 2H), 3.05(q, 2H), 5.53(s, 2H), 6.72(d, 1H), 7.01(d, 2H), 7.26(d, 2H), 7.56(m, 4H), 8.21(d, 1H); mass spectrum (+ve FAB, methanol/nitrobenzyl alcohol): 438$(M+H)^+$; microanalysis, found: C, 67.1; H, 5.4; N, 21.5%; $C_{25}H_{23}N_7O.0.5H_2O$ requires: C, 67.2; H, 5.4; N, 21.9%.

The necessary starting materials of formula IVa used in Examples 2-7, corresponding to starting material A in Example 1, were obtained in yields of 30-75% using a similar procedure to that described in Example 1, part (i) as follows:-

(Example 2A): **2,6-dimethyl-4-[N-methyl-N-(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]pyrimidine** as a solid, m.p. 155°C (decomposition); NMR (CDCl3): 2.31(s, 3H), 2.51(s, 3H), 2.65(s, 3H), 4.72(s, 2H), 6.07(s, 1H), 6.6-6.92(m, 6H), 6.93(d, 2H), 7.09(d, 2H), 7.15-7.4(complex m, 10H), 7.45(m, 2H), 7.95(m, 1H); mass spectrum (+ve FAB, DMSO/methanol/nitrobenzyl alcohol): 614$(M+H)^+$.

(Example 3A): **2-ethyl-4-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)-biphenyl-4-ylmethyl)amino]-5,6,7,8-tetrahydroquinazoline** as a solid, m.p. 190-192°C; NMR ($CDCl_3$): 1.32(t, 3H), 1.75(m, 4H), 2.08(m, 2H), 2.69(m, 2H), 2.74(q, 2H), 4.5(broad t, 1H), 4.64(d, 2H), 6.91(m, 6H), 7.10(s, 4H), 7.25(complex m, 10H), 7.48(m, 2H), 7.95(m, 1H).

(Example 4A): 2,6-dimethyl-5-iodo-4-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]pyrimidine as a solid; NMR ($CDCl_3$): 2.48(s, 3H), 2.57(s, 3H), 4.62(d, 2H), 5.55(broad t, 1H), 6.92(m, 6H), 7.10(m, 4H), 7.26(complex m, 10H), 7.48(m, 2H), 7.95(m, 1H).

(Example 5A): 2-ethyl-4-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]quinazoline as a foam; NMR ($CDCl_3$): 1.39(t, 3H), 2.92(q, 2H), 4.79(d, 2H), 5.55(broad t, 1H), 6.90(m, 6H), 7.26(complex m, 15H), 7.41(m, 1H), 7.48(m, 2H), 7.67(m, 1H), 7.80(d, 1H), 7.98(m, 1H).

(Example 6A): 4-amino-2,6-diethyl-5-iodopyrimidine (320 mg) was added to a mixture of potassium t-butoxide (130 mg) and 1,4,7,10,13,16-hexaoxacyclooctadecane (20 mg) in THF (25 ml) and the mixture was stirred for 5 minutes. A solution of 5-[2-(4'-bromomethylbiphenyl)]-2-triphenylmethyl-2H-tetrazole (111 mg) in tetrahydrofuran (THF) (2 ml) was added and the mixture was stirred for 4 hours. Solvent was removed by evaporation and the residue was partitioned between ethyl acetate and saturated sodium chloride solution. The aqueous layer was separated, extracted with ethyl acetate and the combined organic extracts dried. Solvent was removed by evaporation and the residue was purified by flash chromatography eluting with diethyl ether/hexane (2:3 v/v) to give 2,6-diethyl-5-iodo-4-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-ylmethyl)-amino]pyrimidine as a foam; NMR ($CDCl_3$): 1.25(double t, 6H), 2.82(d of q, 4H), 4.36(d, 2H), 5.68(broad s, 1H), 6.92(m, 6H), 7.09(s, 4H), 7.26(complex m, 8H), 7.38(m, 2H), 7.47(m, 2H), 7.95(m, 1H).

(Example 7A): 2,4-diethyl-8-[(2'-(2-triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-ylmethyl)]pyrido[2,3-d]pyrimidin-7(8H)-one, was obtained using an analogous procedure to that described in Example 6A, as a solid; NMR ($CDCl_3$): 1.35(t, 6H), 3.0(d of q, 4H), 5.60(s, 2H), 6.69(d, 1H), 6.93(m, 6H), 7.04(d, 2H), 7.35(complex m, 14H), 7.83(d, 1H), 7.89(m, 1H).

The necessary starting materials of formula V used in

Examples 2-4, corresponding to compound B in Example 1, were obtained as follows:

(Example 2B): An 8M solution of methylamine in ethanol (6.2 ml) was added to a solution of 6-chloro-2,4-dimethyl pyrimidine (1.42 g) (obtained as described in Chem. Ber., 1902, 35, 1576) in ethanol (5 ml) and the mixture was stirred for 16 hours. Solvent was removed by evaporation and the residue was partitioned between 0.25M sodium carbonate solution (50 ml) and ethyl acetate (25 ml). The aqueous phase was separated and extracted with ethyl acetate (2 x 25 ml). The combined organic extracts were washed with saturated sodium chloride solution and dried. Solvent was removed by evaporation and the residue was triturated with ethyl acetate to give 2,6-dimethyl-4-(N-methylamino)pyrimidine (1.07 g), as a pale yellow solid; NMR ($CDCl_3$): 2.33(s, 3H), 2.47(s, 3H), 2.09 and 2.92(two s, 3H), 5.2(broad s, 1H), 6.00(s, 1H); mass spectrum (CI, ammonia): $138(M+H)^+$.

(Example 3B): (i) A solution of propionamidine hydrochloride (2.7 g) in ethanol (25 ml) was added to a solution of sodium (600 mg) in ethanol (25 ml) and the mixture was stirred for 10 minutes. Ethyl cyclohexanone-2-carboxylate (4.25 g) was added and the mixture was stirred for two days and then heated at reflux for 1 hour. Solvent was removed by evaporation and ice was added to the residue. The mixture was then extracted with ethyl acetate (2 x 50 ml). The combined extracts were washed with water, saturated sodium chloride solution and then dried ($MgSO_4$). Solvent was removed by evaporation and the residue was triturated with hexane. The resultant solid was collected by filtration to give 4-hydroxy-2-ethyl-5,6,7,8-tetrahydroquinazoline (C) (1.1 g), as a solid, m.p. 199-200°C; NMR ($CDCl_3$): 1.33(t, 3H), 1.77(m, 4H), 2.5(m, 2H), 2.66(m, 4H), 12.5(broad s, 1H); mass spectrum (CI, ammonia): $179(M+H)^+$.

(ii) A solution of compound C (100 mg) in phosphorous oxychloride (2 ml) was heated at reflux for 45 minutes. The mixture was cooled to ambient temperature and volatile material was removed by evaporation. Ice was added to the residue and the mixture was basified with sodium bicarbonate. The mixture was extracted with ethyl acetate and the

extract dried ($MgSO_4$). Solvent was removed by evaporation to give 4-chloro-2-ethyl-5,6,7,8-tetrahydroquinazoline (D) (92 mg), as a low melting solid; NMR ($CDCl_3$): 1.33(t, 3H), 1.66(m, 4H), 2.69(m, 2H), 2.85(m, 4H); mass spectrum (CI, ammonia): 196,198$(M+H)^+$.

(iii) Compound D (4.7 g) was added to a saturated solution of ammonia in ethanol (50 ml) and the mixture was heated at 135°C in a sealed tube for 12 hours. Volatile material was removed by evaporation and the residue was partitioned between ethyl acetate and water. The organic layer was separated and solvent was removed by evaporation. The residue was purified by flash chromatography eluting with ethyl acetate/methanol (9:1 v/v) to give 4-amino-2-ethyl-5,6,7,8-tetrahydroquinazoline (2.1 g), as a solid, m.p. 184°C; NMR (d_6-DMSO): 1.15(t, 3H), 1.7(m, 4H), 2.25(broad s, 2H), 2.5(m, 4H), 6.25(broad s, 2H); mass spectrum (CI, ammonia): 178$(M+H)^+$.

(Example 4B): Bis(trifluoroacetoxy)iodobenzene (4.3 g) and iodine (1.27 g) were added to a solution of 4-amino-2,6-dimethylpyrimidine (1.23 g) in dichloromethane (30 ml) and methanol (70 ml) and the mixture was stirred for 16 hours. Solvent was removed by evaporation and 5% sodium metabisulphite solution (50 ml) was added to the residue. The mixture was basified with sodium bicarbonate and the resultant solid was collected by filtration to give 6-iodo-2,4-dimethylpyrimidine (1.5 g), as a yellow solid, m.p. 133-134°C; NMR (d_6-DMSO): 2.26(s, 3H), 2.40(s, 3H), 6.73(broad s, 2H); mass spectrum (CI, ammonia): 250$(M+H)^+$.

(Example 5B): (i) A mixture of 2-aminobenzamide (13.6 g), methyl propionylacetate (26.6 ml) and p-toluenesulphonic acid (150 mg) in benzene (200 ml) was heated at reflux for 6 hours with azeotropic removal of water. The mixture was cooled to ambient temperature and solvent was removed by evaporation. The residue was dissolved in a eutectic mixture of diphenyl/diphenyl ether (1:2.77 v/v) (10 ml) and the solution was added to a refluxing eutectic mixture of diphenyl/diphenyl ether (1:2.77 v/v) (40 ml). The mixture was heated at reflux for 20 minutes and then cooled to ambient temperature. Hexane (200 ml) was added and the mixture was then decanted to leave a

solid residue. The residue was washed with hexane (2 x 200 ml) and collected by filtration to give 2-ethyl-4-hydroxyquinazoline (C) (16.9 g), as a brown solid, m.p. 199-201°C; NMR (d_6-DMSO): 1.25(t, 3H), 2.64(q, 2H), 7.4(m, 1H), 7.6(d, 1H), 7.78(m, 1H), 8.06(dd, 1H), 12.12(broad s, 1H).

(ii) A solution of compound C (1 g) in phosphorous oxychloride (12 ml) was heated at reflux for 1 hour. The mixture was cooled to ambient temperature and volatile material was removed by evaporation. Ice was added to the residue and the mixture was basified with potassium carbonate. The mixture was extracted with ether (2 x 10 ml) and the combined extracts dried ($MgSO_4$). Decolourising activated carbon was added to the ethereal solution and the carbon was then removed by filtration. Solvent was removed by evaporation to give 4-chloro-2-ethylquinazoline (D) (500 mg), as a yellow solid; NMR ($CDCl_3$): 1.4(t, 3H), 3.10(q, 2H), 7.64(m, 1H), 7.98(m, 2H), 8.23(dd, 1H); mass spectrum (CI, ammonia): 192,194$(M+H)^+$.

(iii) Compound D (600 mg) was added to a saturated solution of ammonia in ethanol (25 ml) and the mixture was heated at 180°C for 18 hours. Volatile material was removed by evaporation and saturated sodium bicarbonate solution (25 ml) was added to the residue. The resultant solid was collected by filtration to give 4-amino-2-ethyl-quinazoline (B) (250 mg), as an off white solid, m.p. 214-216°C (decomposition); NMR ($CDCl_3$): 1.39(t, 3H), 2.87(q, 2H), 5.58(broad s, 2H), 7.44(m, 1H), 7.75(m, 3H); mass spectrum (CI, ammonia): 174$(M+H)^+$.

(Example 6B): (i) 4-chloro-2,6-diethylpyrimidine (0.86 g) (obtained as described in J. Chem. Soc., 1963, 5642) was added to a saturated solution of ammonia in ethanol (50 ml) and the mixture was heated at 135°C in a sealed tube for 16 hours. The mixture was cooled to ambient temperature and solvent was removed by evaporation. The residue was triturated with diethyl ether (3 x 2.5 ml) to give 4-amino-2,6-diethylpyrimidine hydrochloride (C) (0.57 g), as an off white solid; NMR (d_6-DMSO): 1.18(d of t, 6H), 2.55(q, 2H), 2.66(q, 2H), 7.6(broad s, 1H); mass spectrum (CI, ammonia): 152$(M+H)^+$.

(ii) Using an analogous procedure to that described in Example 4B, but starting from compound (C), there was obtained in 38% yield 4-amino-2,6-diethyl-5-iodopyrimidine as a solid; NMR ($CDCl_3$): 1.28(d of t, 6H), 2.71(q, 2H), 2.85(q, 2H), 5.42(broad s, 2H); mass spectrum (CI, ammonia): $278(M+H)^+$.

(Example 7B): (i) Iodine (20.3 g) was added to a solution of 2,6-diethyl-4-hydroxypyrimidine (15.2 g) (obtained as described in J. Chem. Soc., 1963, 5642) in 1M sodium hydroxide solution (105 ml) and the mixture stirred for 2 hours. The product was collected by filtration, washed with water and dried to give 2,6-diethyl-4-hydroxy-5-iodopyrimidine (C) (14.6 g) as an off white solid, m.p. 166-168°C; NMR (d_6-DMSO): 1.13(d of t, 6H), 2.51(q, 2H), 2.70(q, 2H), 12.53(broad s, 1H); mass spectrum (CI, ammonia): $279(M+H)^+$.

(ii) A mixture of compound C (556 mg), ethyl acrylate (0.33 ml), palladium (II) acetate (50 mg) and triethylamine (1 ml) in DMF (3 ml) was heated at 120°C for 6 hours. The mixture was cooled to ambient temperature and triturated with saturated sodium carbonate solution. The product was collected by filtration and re-crystallised from ethyl acetate to give ethyl 3-[(2,6-diethyl-4-hydroxy)pyrimidin-5-yl]-acrylate (D) (200 mg) as an off white solid, m.p. 171-174°C; NMR (CDCl3): 1.33(t of t, 9H), 2.80(d of q, 4H), 4.26(q, 2H), 7.30(d, 1H), 7.70(d, 1H); mass spectrum (CI, ammonia): $268(M+NH_4)^+$, $251(M+H)^+$.

(iii) A solution of compound D (1 g) in phosphorous oxychloride (10 ml) was heated at reflux for 1 hour. The mixture was cooled to ambient temperature and volatile material was removed by evaporation. Ice was added to the residue and the mixture was then basified with potassium carbonate. The mixture was extracted with ether (3 x 50 ml) and the combined extracts dried ($MgSO_4$). Solvent was removed by evaporation and the residue purified by flash chromatography eluting with ethyl acetate/hexane (1:9 v/v) to give ethyl 3-[(4-chloro-2,6-diethyl)pyrimidin-3-yl]acrylate (E) (720 mg) as an oil; NMR ($CDCl_3$): 1.32(t of t, 9H), 2.89(d of q, 4H), 4.30(q, 2H), 6.35(d, 1H), 7.71(d, 1H); mass spectrum (CI, ammonia): $268,270(M+H)^+$.

(iv) Compound E (700 mg) was added to a saturated solution of ammonia in ethanol (50 ml) and the mixture was heated at 120°C for 12 hours in a sealed tube. The mixture was cooled to ambient temperature and solvent was removed by evaporation. The residue was triturated with acetone and the solid was removed by filtration and discarded. The filtrate was concentrated by evaporation and the residue was purified by flash chromatography to give ethyl 3-[(4-amino-2,6-diethyl)pyrimidin-5-yl]acrylate (F) (220 mg) as an oil; NMR ($CDCl_3$): 1.30(t of t, 9H), 2.73(d of q, 4H), 4.28(q, 2H), 5.07(broad s, 2H), 6.29(d, 1H), 7.73(d, 1H); mass spectrum (CI, ammonia): 250$(M+H)^+$.

(v) Compound F (50 mg) was added to a solution of sodium (18 mg) in ethanol (10 ml) and the mixture heated at reflux for 2 hours. The mixture was cooled to ambient temperature and solvent was removed by evaporation. Saturated sodium chloride solution (10 ml) was added to the residue and the mixture was acidified to pH 4 with 1M citric acid solution. The mixture was then extracted with dichloromethane (2 x 10 ml) and the combined extracts dried ($MgSO_4$). Solvent was removed by evaporation to give 2,4-diethylpyrido[2,3-d]pyrimidin-7(8H)-one (B) (22 mg), as a foam; NMR ($CDCl_3$): 1.37(t, 6H), 3.01(d of q, 4H), 6.66(d, 1H), 7.89(d, 1H), 9.57(broad s, 1H); mass spectrum (CI, ammonia): 204$(M+H)^+$.

EXAMPLES 8-11

Using an analogous procedure to that described in Example 1, but starting from the appropriate compound corresponding to starting material A in Example 1, the following compounds were obtained in yields of 53-85%:

(Example 8): 2,4-diethyl-8-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-7-one hydrochloride as a solid, m.p. 240-241°C; NMR (d_6-DMSO): 1.2(dt, 6H), 2.85(m, 6H), 2.99(q, 2H), 5.22(s, 2H), 7.01(d, 2H), 7.24(d, 2H), 7.60(m, 4H); mass spectrum (+ve FAB, methanol/nitrobenzyl alcohol): 462$(M+Na)^+$, 440$(M+H)^+$; microanalysis, found: C, 62.4; H, 5.5; N, 19.7%; $C_{25}H_{27}N_7O.1.0HCl.0.1(C_2H_5)_2O$ requires: C, 62.1; H, 5.5; N, 19.9%.

(Example 9): 2,6-diethyl-5-(4-methylphenyl)-4-[(2'-(1H-tetrazol-5-yl)methylamino]pyrimidine hydrochloride as a solid m.p. 246°C; NMR (d_6-DMSO): 1.05(t, 3H), 1.24(t, 3H), 2.39(q, 2H), 2.40(s, 3H), 2.86(q, 2H), 4.60(d, 2H), 7.03(d, 2H), 7.20(d, 4H), 7.39(d, 2H), 7.48(m, 4H), 8.30(t, 1H); mass spectrum (+ve FAB, methanol/nitrobenzyl alcohol): 476 $(M+H)^+$; microanalysis, found: C, 67.9; H, 6.0; N, 19.3%; $C_{29}H_{29}N_7.1.0HCl$ requires: C, 68.0; H, 5.9; N, 19.1%.

(Example 10): 2,6-diethyl-5-(phenylmethyl)-4-[(2'-(1H-tetrazol-5-yl)methylamino]pyrimidine hydrochloride as a solid, m.p. 202-203°C; NMR (d_6-DMSO): 1.02(t, 3H), 1.15(t, 3H), 2.5(q, 2H), 2.55(q, 2H), 3.93(s, 2H), 4.58(d, 2H), 6.95(d, 2H), 7.07(d, 4H), 7.2(m, 3H), 7.55(m, 5H); mass spectrum (+ve FAB, methanol/nitrobenzyl alcohol): 476 $(M+H)^+$; microanalysis, found: C, 70.4; H, 6.4; N, 19.6%; $C_{29}H_{29}N_7.1.0HCl.1.0H_20$ requires: C, 70.5; H, 6.3; N, 19.8%.

(Example 11): 2,4-diethyl-8-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)-methyl]-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine hydrochloride as a solid, m.p. 255-256°C; NMR (d_6-DMSO): 1.20(dt, 6H), 1.88(m, 2H), 2.70(m, 6H), 3.55(m, 2H), 4.98(s, 2H), 7.08(d, 2H), 7.27(d, 2H), 7.60(m, 4H); mass spectrum (+ve FAB, methanol/nitrobenzyl alcohol): 426 $(M+H)^+$; microanalysis, found: C, 64.1; H, 5.9; N, 20.1%; $C_{25}N_{27}N_5.1.0.HCl.0.15(C_2H_5)_20$ requires: C, 64.3; H, 6.0; N, 20.5%.

The necessary starting materials of formula IVa used in Examples 8-11, corresponding to starting material A in Example 1, were obtained in yields of 28-75% as follows:

(Example 8A): Using an analogous procedure to that described in Example 6A there was thus obtained 2,4-diethyl-8-[(2'-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-7-one as a foam; NMR ($CDCl_3$): 1.24(t, 3H), 1.32(t, 3H), 2.8(m, 8H), 5.26(s, 2H), 6.9(m, 6H), 7.03(d, 2H), 7.28(complex m, 12H), 7.45(m, 2H), 7.89(m, 1H).

(Example 9A): Using an analogous procedure to that described in Example 6A there was thus obtained 2,6-diethyl-5-(4-methylphenyl)-4-

[(2′-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methylamino]-pyrimidine as a foam; NMR ($CDCl_3$): 1.10(t, 3H), 1.35(t, 3H), 2.36(s, 3H), 2.40(q, 2H), 2.83(q, 2H), 4.95(d, 2H), 4.6(bs, H), 6.90(complex m, 8H), 7.05(complex m, 7H), 7.25(complex m, 9H), 7.45(m, 2H), 7.90(m, 1H).

(Example 10A): Using an analogous procedure to that described in Example 6A there was thus obtained 2,6-diethyl-5-(phenylmethyl)-4-[2-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methylamino]-pyrimidine as a foam; NMR ($CDCl_3$): 1.31(dt, 6H), 3.0(broad s, 4H), 3.81(s, 1H), 4.57(d, 2H), 6.73(d, 2H), 6.90(complex m, 6H), 7.00(complex m, 4H), 7.10(s, 1H), 7.26(complex m, 11H), 7.50(m, 3H), 7.91(m, 1H); mass spectrum (+ve FAB, DMSO/nitro benzyl alcohol): 718 $(M+H)^+$.

(Example 11A): Using an analogous procedure to that described in Example 1, part (i), 2,4-diethyl-8-[2′-(2-triphenylmethyl-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5,6,7,8-tetrahydropyrido[2,3-d]-pyrimidine as a foam; NMR ($CDCl_3$): 1.25(dt, 6H), 1.8(m, 2H), 2.59(m, 4H), 2.72(q, 2H), 3.13(m, 2H), 4.82(s, 2H), 6.9(m, 6H), 7.07(s, 3H), 7.15-7.5(complex m, 14H), 7.92(m, 1H); mass spectrum (+ve FAB, methanol/nitrobenzyl alcohol): 668 $(M+H)^+$.

The necessary starting materials of formula V used in Examples 8-11 corresponding to B in Example 1 were prepared as follows:-

(Example 8B): (i) A solution of ethyl 3-[(4-amino-2,6-diethyl)-pyrimidin-5-yl]acrylate (100 mg) in ethanol (6 ml) was catalytically hydrogenated over 30% palladium on carbon. When hydrogen uptake ceased the catalyst was removed by filtration through diatomaceous earth. Solvent was removed from the filtrate by evaporation to give ethyl 3-[(4-amino-2,6-diethyl)pyrimidin-5-yl]propionate (B) (88 mg) as an oil; NMR ($CDCl_3$): 1.18(m, 9H), 2.6(m, 8H), 4.09(q, 2H), 5.09(broad s, 2H); mass spectrum (chemical ionisation, ammonia): 252 $(M+H)^+$,

(ii) Sodium metal (27 mg) was added to a solution of compound B

(290 mg) in ethanol (15 ml) and the mixture was stirred at ambient temperature for 2 hours. Solvent was removed by evaporation and the residue was partitioned between water (5 ml) and ethyl acetate (20 ml). The aqueous layer was separated and extracted with ethyl acetate (20 ml). The combined organic solutions were dried ($MgSO_4$) and solvent removed by evaporation to give 2,4-diethyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-7-one (C) (205 mg) as a pale pink solid, m.p. 93-96°C; NMR ($CDCl_3$): 1.30(dt, 6H), 2.86(m, 8H), 8.02(broad s, 2H); mass spectrum (chemical ionisation, ammonia): 206 $(M+H)^+$.

(Example 9B): (i) A solution of 2,6-diethyl-4-hydroxy-5-iodopyrimidine (1.0 g) in phosphorus oxychloride (10 ml) was heated at reflux for 2 hours. The solution was cooled to ambient temperature and volatile material was removed by evaporation. The residue was treated with water (100 ml) and the mixture basified with solid potassium carbonate. The mixture was extracted with ether (2 x 50ml) and the combined organic extracts dried ($MgSO_4$). Solvent was removed by evaporation to give 4-chloro-2,6-diethyl-5-iodopyrimidine (C) (1.01 g); NMR ($CDCl_3$): 1.31 (dt, 6H), 2.94(dq, 4H); mass spectrum (chemical ionisation, ammonia): 296, 298 $(M+H)^+$.

(ii) A mixture of compound C (0.72 g), 4-methylphenyl boronic acid (0.35 g), tetrakis(triphenylphosphine)palladium (86 mg), saturated sodium bicarbonate solution (12 ml) and toluene (40 ml) was heated under reflux for 6 hours. The mixture was cooled to ambient temperature and the organic phase was separated. The aqueous layer was extracted with ethyl acetate and the combined organic phases were dried ($MgSO_4$) and solvent was removed by evaporation. The residue was purified by flash chromatography eluting with ethyl acetate/hexane (1:9 v/v) to give 4-chloro-2,6-diethyl-5-(4-methylphenyl)pyrimidine (D) (0.42 g) as a solid; NMR ($CDCl_3$): 1.13(t, 3H), 1.39(t, 3H), 2.56(q, 2H), 2.97(q, 2H), 7.10(d, 2H), 7.27(d, 2H); mass spectrum (chemical ionisation, ammonia): 261 $(M+H)^+$.

(iii) Compound D (0.40 g) was added to a saturated solution of ammonia in ethanol (10 ml) and the mixture was heated at 150°C for 12

hours. Volatile material was removed by evaporation and the residue was partitioned between saturated sodium bicarbonate solution (5 ml) and ethyl acetate (20 ml). The aqueous layer was separated, extracted with ethyl acetate (20 ml) and the combined organic extracts dried ($MgSO_4$). Solvent was removed by evaporation and the residue was purified by flash chromatography eluting with ethyl acetate to give 4-amino-2,6-diethyl-5-(4-methylphenyl)pyrimidine (E) (0.2 g) as a solid, m.p. 110-114°C; NMR ($CDCl_3$): 1.10(t, 3H), 1.35(t, 3H), 2.41(s, 3H), 2.42(q, 2H), 2.78(q, 2H), 4.62(broad s, 2H), 7.12(d, 2H), 7.27(d, 2H); mass spectrum (chemical ionisation, ammonia): 242 $(M+H)^+$.

(Example 10B): (i) Benzyl bromide (1.18 ml) was added to a suspension of zinc dust (1.0 g) in THF (25 ml) containing dibromoethane (20 mg) and the mixture was stirred at ambient temperature for 1 hour. 4-Chloro-2,6-diethyl-5-iodopyrimidine (0.9 g) and tetrakis(triphenylphosphine) palladium (0.1 g) were added and the mixture was heated at reflux for 4 hours under an argon atmosphere. The mixture was cooled to ambient temperature and insoluble material was removed by filtration. The filtrate was extracted with saturated ethylenediamine tetracetic acid solution and the organic phase separated and dried ($MgSO_4$). Volatile material was removed by evaporation and the residue was purified by flash chromatography eluting with ethyl acetate/hexane (1:9 v/v) to give 4-chloro-2,6-diethyl-5-(phenylmethyl) pyrimidine (C) (0.5 g) as an oil; NMR ($CDCl_3$): 1.19(t, 3H), 1.38(t, 3H), 2.74(q, 2H), 2.93(q, 2H), 4.18(s, 2H), 7.08(d, 2H), 7.27(m, 3H).

(ii) Compound C (0.5 g) was added to a saturated solution of ammonia in ethanol (15 ml) and the mixture was heated at 150°C for 18 hours. Volatile material was removed by evaporation and the residue was purified by flash chromatography eluting with ethyl acetate to give 4-amino-2,6-diethyl-5-(phenylmethyl)pyrimidine) (0.15 g) as an oil; NMR ($CDCl_3$) 1.28(dt, 6H), 2.77(dq, 4H), 3.91(s, 2H), 4.67(broad s, 2H), 7.13(m, 2H), 7.28(m, 3H); mass spectrum (chemical ionisation, ammonia): 242 $(M+H)^+$.

(Example 11B): A solution of 2,4-diethyl-5,6,7,8-tetrahydro-

pyrido[2,3-d]pyrimidin-7-one (205 mg) in THF (5 ml) was added dropwise to a suspension of lithium aluminium hydride (40 mg) in THF (10 ml). The mixture was heated at reflux for 1 hour under an atmosphere of argon. The mixture was cooled to ambient temperature and 1M sodium hydroxide solution (1 ml) was added. Volatile material was removed by evaporation and the residue was partitioned between ethyl acetate (20 ml) and water (5 ml). The organic layer was separated and dried ($MgSO_4$). Solvent was removed by evaporation to give 2,4-diethyl-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidine as a solid; NMR ($CDCl_3$): 1.23(dt, 6H), 1.94(m, 2H), 2.62(m, 6H), 3.40(m, 2H), 5.22(broad s, 1H); mass spectrum (chemical ionisation, ammonia): 192 $(M+H)^+$.

EXAMPLE 12

(Note: all parts by weight)

The compounds of the invention may be administered for therapeutic or prophylactic use to warm-blooded animals such as man in the form of conventional pharmaceutical compositions, typical examples of which include the following:-

a) **Capsule** (for oral administration)

Active ingredient *	20
Lactose powder	578.5
Magnesium stearate	1.5

b) **Tablet** (for oral administration)

Active ingredient *	50
Microcrystalline cellulose	400
Starch (pregelatinised)	47.5
Magnesium stearate	2.5

c) **Injectable Solution** (for intravenous administration)

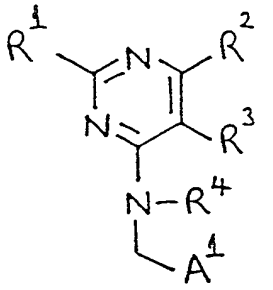
Active ingredient *	0.05 - 1.0
Propylene glycol	5.0
Polyethylene glycol (300)	3.0 - 5.0
Purified water	to 100%

d) **Injectable Suspension** (for intramuscular administration)

Active ingredient *	0.05 - 1.0
Methylcellulose	0.5
Tween 80	0.05
Benzyl alcohol	0.9
Benzalkonium chloride	0.1
Purified water	to 100%

Note: the active ingredient * may typically be an Example described hereinbefore and will conveniently be present as a pharmaceutically acceptable acid-addition salt, such as the hydrochloride salt. Tablets and capsules formulations may be coated in conventional manner in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating.

Chemical Formulae



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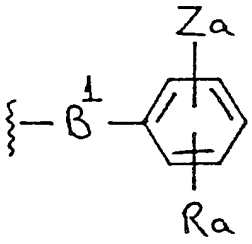

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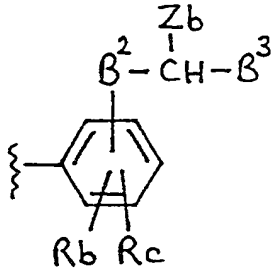

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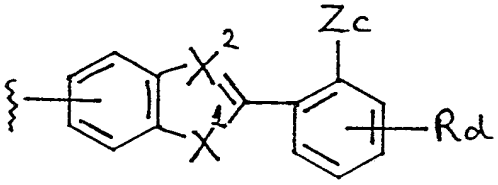

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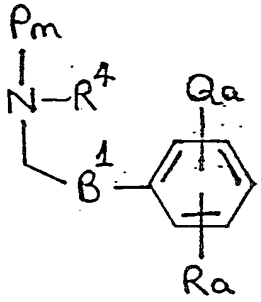

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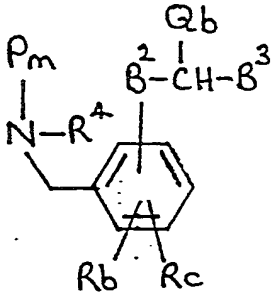

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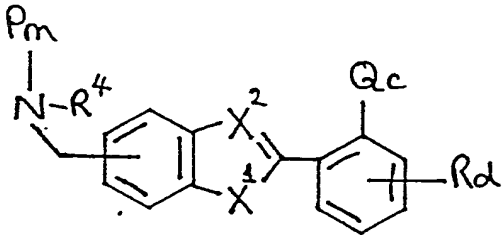

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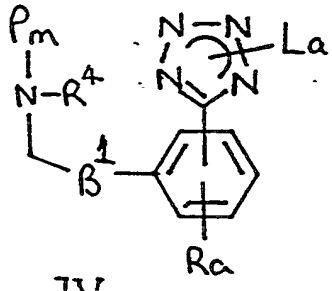

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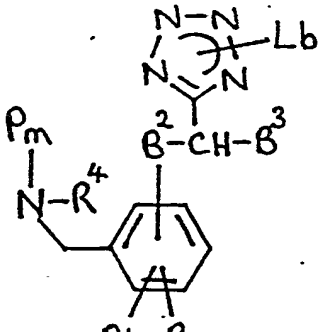

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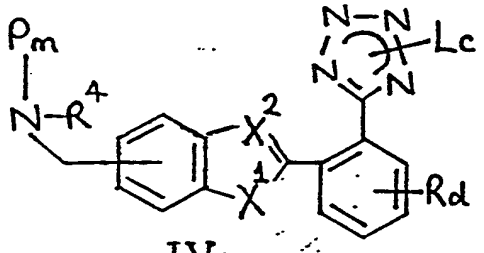
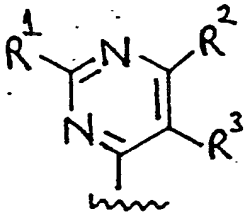


IVc

Note: Pm =



Chemical Formulae

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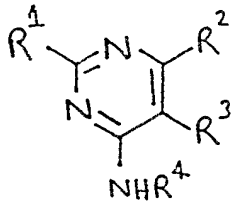
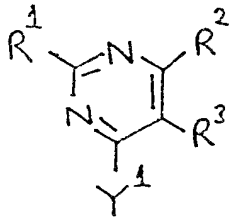
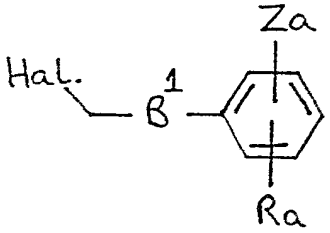
V 

VI 



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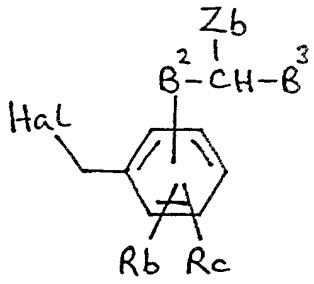

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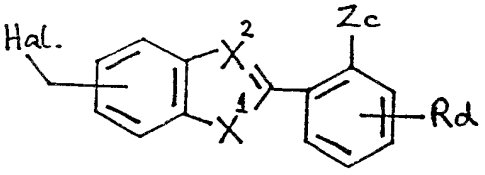

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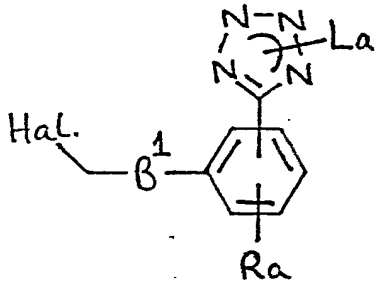

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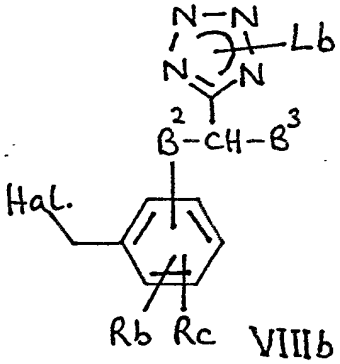

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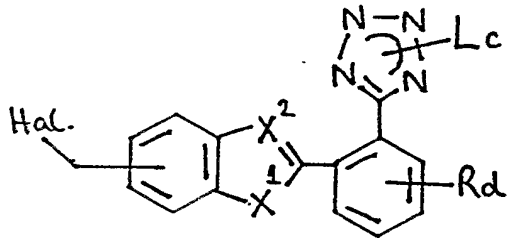

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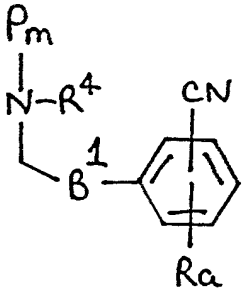

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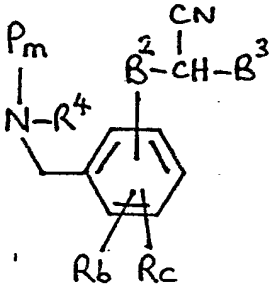

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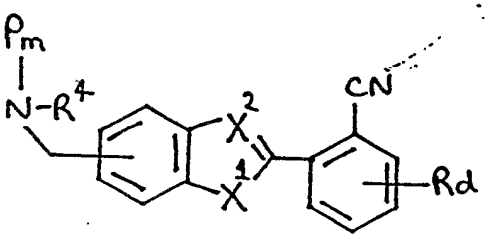

IXc

Chemical Formulae

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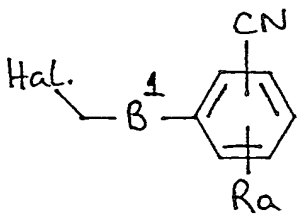

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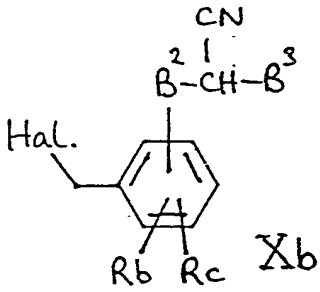

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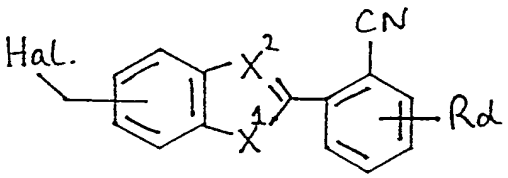

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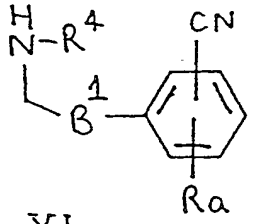

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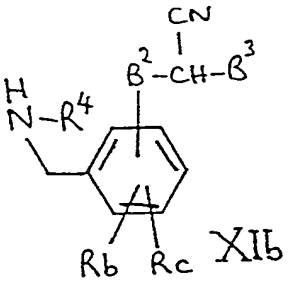

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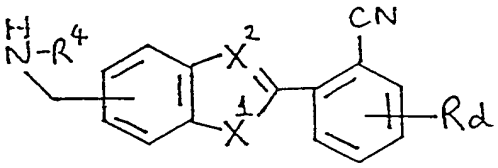

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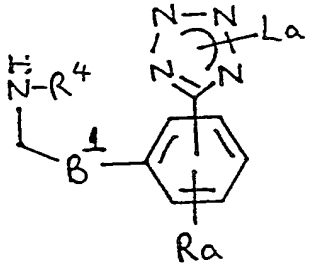

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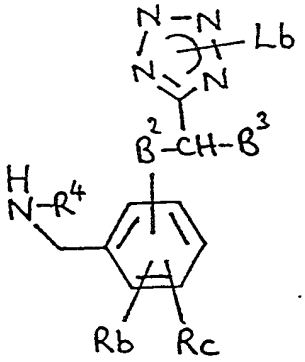

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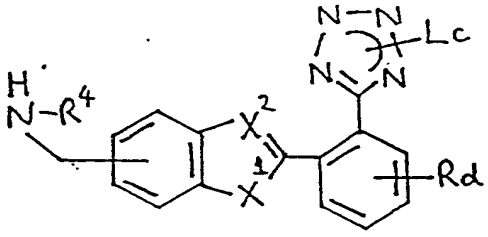

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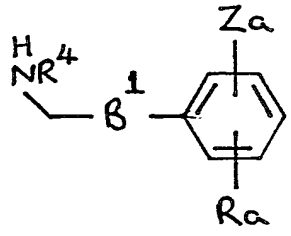

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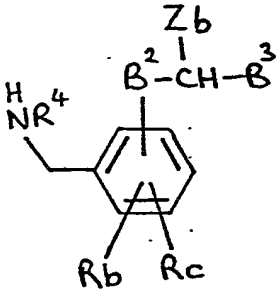

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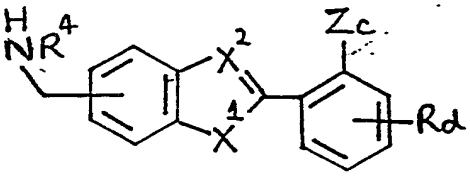

XIIIc

Chemical Formulae
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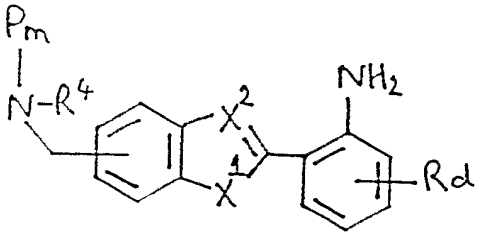

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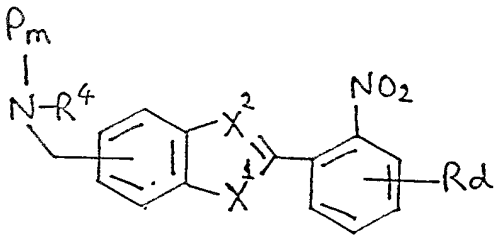

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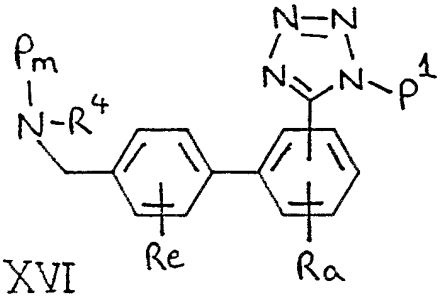

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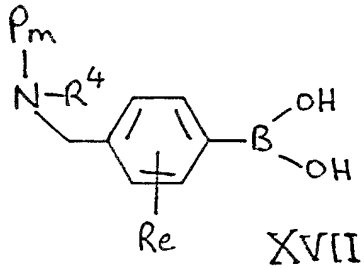

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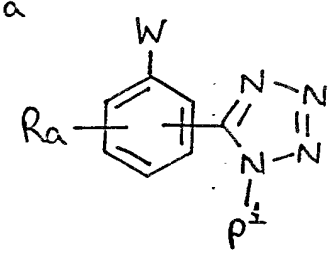
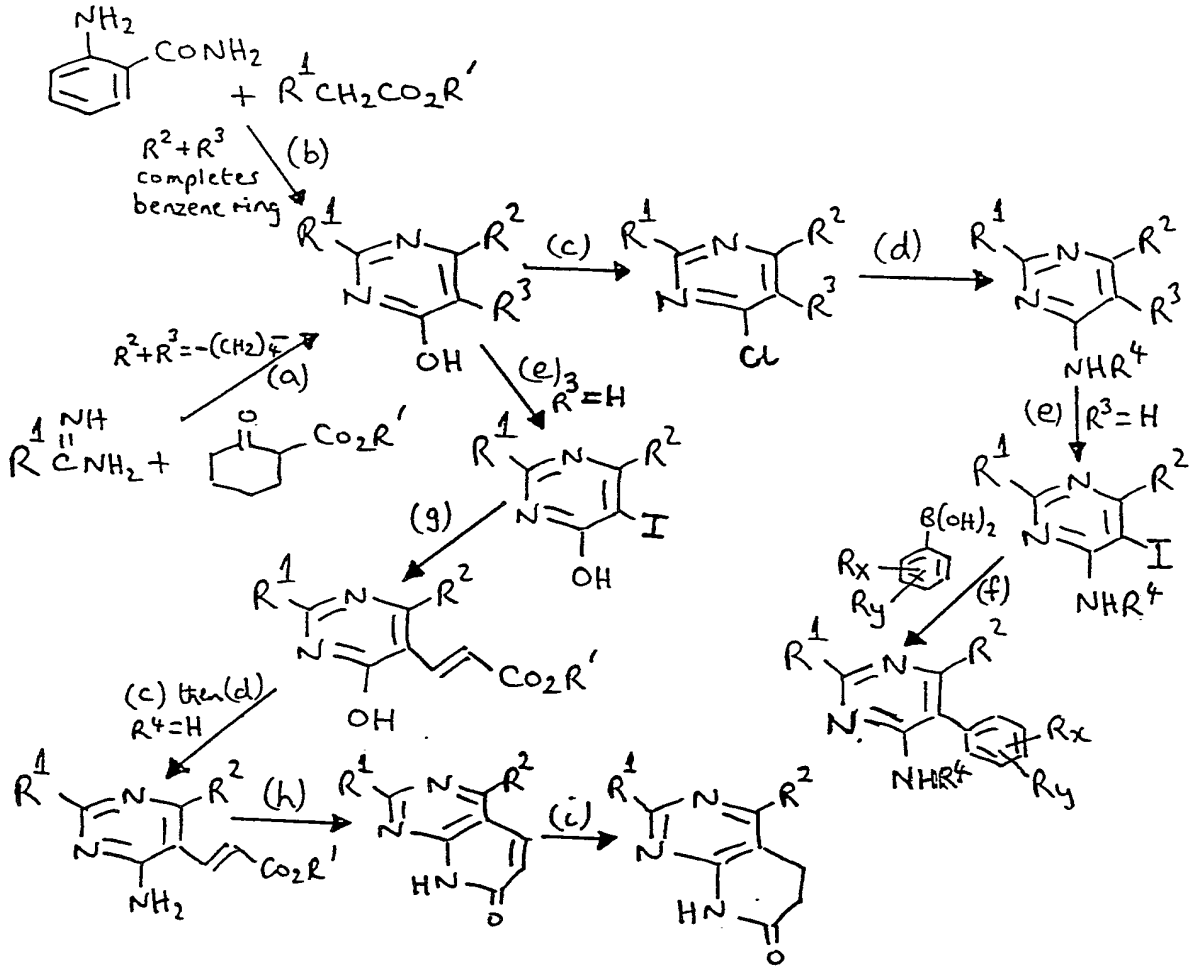


XVIII

Scheme 1



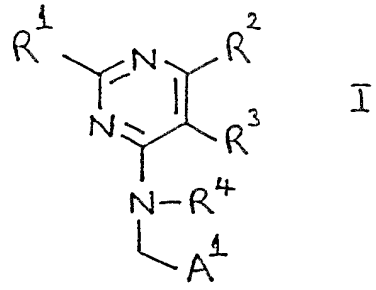
Note: R′ = lower alkyl; Rx and Ry are optional substituents

Reagents:
a) sodium ethoxide, ethanol, ambient temperature
b) p-Toluenesulphonic acid, benzene, reflux with azeotropic removal of water; heat
c) $POCl_3$, reflux
d) R^4NH_2, EtOH, ambient to 180°C
e) bis(trifluoroacetoxy)iodobenzene, I_2, CH_2Cl_2/MeOH
f) tetrakis(triphenylphosphine)palladium, triethylamine, dimethoxyethane
g) ethyl acrylate, Pd(II)acetate, Et_3N, 120°C, DMF
h) sodium ethoxide, ethanol, reflux
i) hydrogenation, palladium on carbon

CLAIMS

What is claimed is:-

1. A pyrimidine derivative of the formula I



I

wherein R^1 is hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, phenyl or substituted (1-4C)alkyl, the latter containing one or more fluoro substituents or bearing a (3-8C)cycloalkyl, (1-4C)alkoxy or phenyl substituent;
R^2 is (1-8C)alkyl, (3-8C)cycloalkyl, phenyl or substituted (1-4C)alkyl, the latter containing one or more fluoro substituents or bearing a (3-8C)cycloalkyl, (1-4C)alkoxy or phenyl substituent, halogeno, (1-4C)alkoxy, amino and alkylamino and dialkylamino of up to 6 carbon atoms;
R^3 is selected from hydrogen, (1-8C)alkyl, (3-8C)cycloalkyl, substituted (1-4C)alkyl bearing a (3-8C)cycloalkyl, amino, hydroxy, (1-4C)alkoxy, carboxy or (1-4C)alkoxycarbonyl substituent or containing one or more fluoro substituents, hydroxy(1-4C)alkoxy, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, carbamoyl, (1-4C)alkanoyl, N-alkylcarbamoyl and di-(N-alkyl)carbamoyl of up to 7 carbon atoms, halogeno, amino, alkylamino and dialkylamino of up to 6 carbon atoms, (1-4C)alkanoylamino, phenyl, phenyl(1-4C)alkyl and benzoyl, the benzene ring of which last three groups optionally bearing one or two substituents selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl, nitro, hydroxy, carboxy, (1-4C)alkanoylamino, (1-4C)alkanoyl, fluoro(1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, carbamoyl, alkyl or dialkylcarbamoyl of up to 7 carbon atoms,

sulphamoyl, N-alkyl or di-(N-alkyl)sulphamoyl of up to 6 carbon atoms, (1-4C)alkoxycarbonyl, (1-4C)alkanesulphonamido, (1-4C)alkyl.$S(O)_n$- [in which n is zero, 1 or 2], 1H-tetrazol-5-yl, phenyl, phenoxy, benzyloxy, benzyloxycarbonyl, benzamido and benzenesulphonamido, the benzene moiety of the last six groups optionally bearing a halogeno, (1-4C)alkyl or (1-4C)alkoxy substituent;

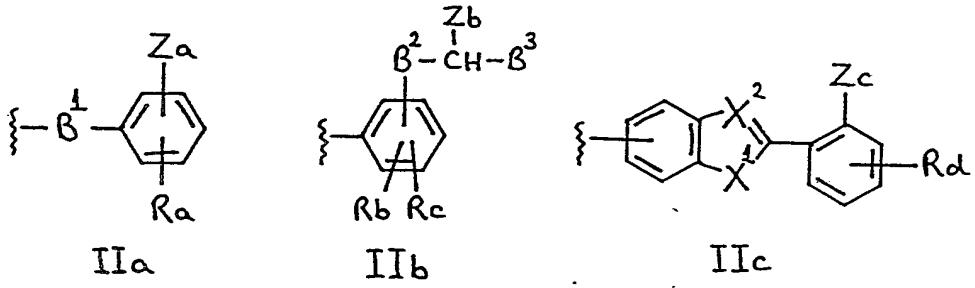
R^4 is hydrogen or (1-4C)alkyl;

or R^2 and R^3 together complete a benzene ring, said benzene ring optionally bearing one or two substituents independently selected from any of the previous values defined for R^3;

or R^2 and R^3 together form an (3-6C)alkenylene group, an (3-6C)alkylene group or an (3-6C)alkylene group in which a methylene is replaced by carbonyl;

or R^3 and R^4 together form a linking group A which is selected from $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CO-CH_2-$, $-CH_2-CO-$, $-CO-CH_2-CH_2-$, $-CH_2-CH_2-CO-$, -CO-CH=CH- and -CH=CH-CO-, and wherein said linking group A optionally bears one or two substituents independently selected from (1-4C)alkyl, substituted (1-4C)alkyl containing one or more fluoro substituents or bearing a (3-8C)cycloalkyl, (1-4C)alkoxy or phenyl substituent, (3-8C)cycloalkyl, (1-4C)alkoxy, halogeno, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, (1-4C)alkanoyl, (1-4C)alkyl.$S(O)_m$- [in which m is zero, 1 or 2] and phenylsulphonyl;

A^1 is a group of the partial formula IIa, IIb or IIc



IIa IIb IIc

wherein

(1) in partial formula IIa, B^1 is a direct bond or is phenylene optionally bearing a substituent selected from (1-4C)alkyl,

(1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano and nitro; Ra is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl or nitro; and Za is 1H-tetrazol-5-yl, a carboxy group or in vivo hydrolysable ester thereof, -CO.NH.(1H-tetrazol-5-yl), or a group of the formula $-CO.NH.CO_2R^8$ in which R^8 is (1-6C)alkyl, (3-8C)cycloalkyl, trifluoromethyl or phenyl;
(2) in partial formula IIb, B^2 is oxygen, sulphur or a group of the formula $-NR^5-$ in which R^5 is hydrogen or (1-4C)alkyl; Zb has any of the values defined above for Za; B^3 is phenyl optionally bearing one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy and halogeno; and Rb and Rc are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy and halogeno; and
(3) in partial formula IIc, Zc is 1H-tetrazol-5-yl, carboxy or in vivo hydrolysable ester thereof or a group of the formula CF_3SO_2NH-; Rd is selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro; X^1 is oxygen, sulphur or a group of the formula $-NR^6-$ in which R^6 is hydrogen or (1-4C)alkyl; and X^2 is nitrogen or is a group of the formula $-C(R^7)=$ wherein R^7 is hydrogen, (1-4C)alkyl optionally containing one or more fluoro substituents, carbamoyl or N-alkyl or di-(N-alkyl)carbamoyl of up to 7 carbon atoms, halogeno, cyano, (1-4C)alkoxycarbonyl or (1-4C)alkanoyl;
and wherein any of said phenyl moieties of R^1, R^2 or R^8, or of an optional substituent on linking group A, may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano and trifluoromethyl; or a non-toxic salt thereof; but excluding the compound 4-[N-butyl-N-(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]-2,6-dimethylpyrimidine.

2. A compound as claimed in claim 1 wherein R^1 is hydrogen, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroehyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopentylethyl, 2-methoxyethyl, 2-ethoxyethyl, benzyl, 1-phenylethyl or 2-phenylethyl; R^2 is methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, fluoromethyl, trifluoromethyl,

2,2,2-trifluoroethyl, pentafluoroehyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopentylethyl, 2-methoxyethyl, 2-ethoxyethyl, benzyl, 1-phenylethyl or 2-phenylethyl; R^3 is hydrogen, methyl, ethyl, propyl, butyl, isobutyl, sec-butyl, pentyl, hexyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, cyclopentylethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, aminomethyl, 2-aminoethyl, methoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, carboxymethyl, 1-carboxyethyl, 2-carboxyethyl, methoxycarbonylmethyl, ethoxycarbonylmethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, hydroxymethyloxy, 1-hydroxyethyloxy, 2-hydroxyethyloxy, 3-hydroxypropyloxy, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl, 3-methyl-3-butenyloxycarbonyl, cyano, nitro, carbamoyl, formyl, acetyl, butyryl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, fluoro, chloro, bromo, iodo, amino, methylamino, ethylamino, butylamino, dimethylamino, diethylamino, dipropylamino, formamido, acetamido, propanamido, phenyl, benzyl, 1-phenylethyl, 2-phenylethyl or benzoyl, the benzene ring of which last five groups optionally bearing one or two substituents selected from methyl, ethyl, methoxy, ethoxy, chloro, bromo, iodo, cyano, trifluoromethyl, nitro, hydroxy, carboxy, formamido, acetamido, propanamido, formyl, acetyl, butyryl, trifluoromethoxy, 2-fluoroethoxy, 2,2,2-trifluoroethoxy, 3,3,3-trifluoropropoxy, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 2-methoxyethyl, 2-ethoxyethyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, sulphamoyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, methanesulphonamido, ethanesulphonamido, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl, 1H-tetrazol-5-yl, phenyl, phenoxy, benzyloxy, benzyloxycarbonyl, benzamido and benzenesulphonamido, the benzene moiety of the last six groups optionally bearing a fluoro, chloro, bromo, methyl, ethyl, methoxy or

ethoxy substituent;
R^4 is hydrogen, methyl, ethyl or propyl;
or R^2 and R^3 together complete a benzene ring, said benzene ring optionally bearing one or two substituents independently selected from any of the previous values defined for R^3;
or R^2 and R^3 together form a 1-propenylene, 2-propenylene, 1-butenylene, 2-butenylene, 3-butenylene, trimethylene, tetramethylene, pentamethylene, 1-oxopropylidene, 3-oxopropylidene, 1-oxobutylidene or 4-oxobutylidene group; or R^3 and R^4 together form a linking group A which is selected from $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CO-CH_2-$, $-CH_2-CO-$, $-CO-CH_2-CH_2-$, $-CH_2-CH_2-CO-$, -CO-CH=CH- and -CH=CH-CO-, and wherein said linking group A optionally bears one or two substituents independently selected from methyl, ethyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylethyl, cyclopentylethyl, 2-methoxyethyl, 2-ethoxyethyl, benzyl, 1-phenylethyl, 2-phenylethyl, cyclopropyl, cyclopentyl, cyclohexyl, methoxy, ethoxy, propoxy, fluoro, chloro, bromo, iodo, carboxy, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, allyloxycarbonyl, 2-methyl-2-propenyloxycarbonyl, 3-methyl-3-butenyloxycarbonyl, cyano, nitro, formyl, acetyl, butyryl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, methylsulphonyl, ethylsulphonyl and phenylsulphonyl;
A^1 is a group of the partial formula IIa, IIb or IIc wherein
(1) in partial formula IIa, B^1 is a direct bond or is phenylene optionally bearing a substituent selected from methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, formyl, acetyl, propionyl, trifluoromethyl, cyano and nitro; Ra is hydrogen, methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, trifluoromethyl, cyano or nitro; R^8 is methyl, ethyl, propyl, isopropyl, butyl, pentyl, cyclobutyl, cyclopentyl, cyclohexyl, trifluoromethyl or phenyl;

(2) in partial formula IIb, B^2 is oxygen, sulphur or a group of the formula $-NR^5-$ in which R^5 is hydrogen, methyl, ethyl or propyl;
B^3 is phenyl optionally bearing one or two substituents independently selected from methyl, ethyl, methoxy, ethoxy, fluoro, chloro or bromo; and Rb and Rc are independently selected from hydrogen, methyl, ethyl,

methoxy, ethoxy, fluoro, chloro and bromo; and
(3) in partial formula IIc, Rd is selected from hydrogen, methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, trifluoromethyl, cyano and nitro; X^1 is oxygen, sulphur or a group of the formula $-NR^6-$ in which R^6 is hydrogen, methyl, ethyl or propyl; and X^2 is nitrogen or is a group of the formula $-C(R^7)=$ wherein R^7 is hydrogen, methyl, ethyl, fluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, carbamoyl, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, fluoro, chloro, bromo, iodo, cyano, methoxycarbonyl, ethoxycarbonyl, formyl, acetyl or propionyl;
and wherein any of said phenyl moieties of R^1, R^2 or R^8, or of an optional substituent on linking group A, may be unsubstituted or bear one or two substituents independently selected from methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo, cyano and trifluoromethyl; or a non-toxic salt thereof.

3. A compound as claimed in claim 1 wherein R^1 and R^2 are both (1-8C)alkyl.

4. A compound as claimed in claim 1 or 3 wherein R^1 is (1-8C)alkyl; R^2 is (1-8C)alkyl; R^3 is halogeno; R^4 is hydrogen or (1-4C)alkyl;
or R^2 and R^3 together form an (3-6C)alkylene group;
or R^3 and R^4 together form a linking group A which is selected from $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $-CO-CH_2-$, $-CH_2-CO-$, $-CO-CH_2-CH_2-$, $-CH_2-CH_2-CO-$, $-CO-CH=CH-$ and $-CH=CH-CO-$, and wherein said linking group A optionally bears one or two substituents independently selected from (1-4C)alkyl, substituted (1-4C)alkyl containing one or more fluoro substituents or bearing a (3-8C)cycloalkyl, (1-4C)alkoxy or phenyl substituent, (3-8C)cycloalkyl, (1-4C)alkoxy, halogeno, carboxy, (1-4C)alkoxycarbonyl, (3-6C)alkenyloxycarbonyl, cyano, nitro, (1-4C)alkanoyl, (1-4C)alkyl.$S(O)_m-$ [in which m is zero, 1 or 2] and phenylsulphonyl;
A^1 is a group of the partial formula IIa, IIb or IIc wherein
(1) in partial formula IIa, B^1 is a direct bond or is phenylene optionally bearing a substituent selected from (1-4C)alkyl,

(1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano and nitro; Ra is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl or nitro; and Za is 1H-tetrazol-5-yl, a carboxy group or in vivo hydrolysable ester thereof, -CO.NH.(1H-tetrazol-5-yl), or a group of the formula $-CO.NH.CO_2R^8$ in which R^8 is (1-6C)alkyl, (3-8C)cycloalkyl, trifluoromethyl or phenyl;
(2) in partial formula IIb, B^2 is oxygen, sulphur or a group of the formula $-NR^5-$ in which R^5 is hydrogen or (1-4C)alkyl; Zb has any of the values defined above for Za; B^3 is phenyl optionally bearing one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy and halogeno; and Rb and Rc are independently selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy and halogeno; and
(3) in partial formula IIc, Zc is 1H-tetrazol-5-yl, carboxy or in vivo hydrolysable ester thereof or a group of the formula CF_3SO_2NH-; Rd is selected from hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, trifluoromethyl, cyano and nitro; X^1 is oxygen, sulphur or a group of the formula $-NR^6-$ in which R^6 is hydrogen or (1-4C)alkyl; and X^2 is nitrogen or is a group of the formula $-C(R^7)=$ wherein R^7 is hydrogen, (1-4C)alkyl optionally containing one or more fluoro substituents, carbamoyl or N-alkyl or di-(N-alkyl)carbamoyl of up to 7 carbon atoms, halogeno, cyano, (1-4C)alkoxycarbonyl or (1-4C)alkanoyl;
and wherein any of said phenyl moieties of R^1, R^2 or R^8, or of an optional substituent on linking group A, may be unsubstituted or bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano and trifluoromethyl; or a non-toxic salt thereof.

5. A compound as claimed in claim 3 or 4 wherein R^3 is halogeno.

6. A compound as claimed in claim 1, 3 or 4 wherein R^2 and R^3 together form an (3-6C)alkylene group.

7. A compound as claimed in claim 1 or 3 wherein R^3 is phenyl or benzoyl either of which groups may optionally bear one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl, nitro, hydroxy, carboxy,

(1-4C)alkanoylamino, (1-4C)alkanoyl, fluoro(1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, carbamoyl, alkyl or dialkylcarbamoyl of up to 7 carbon atoms, sulphamoyl, alkyl or dialkylsulphamoyl of up to 6 carbon atoms, (1-4C)alkoxycarbonyl, (1-4C)alkanesulphonamido, (1-4C)alkyl.$S(O)_n$- [in which n is zero, 1 or 2], 1H-tetrazol-5-yl, phenyl, phenoxy, benzyloxy, benzyloxycarbonyl, benzamido and benzenesulphonamido, the benzene moiety of the last six groups optionally bearing a halogeno, (1-4C)alkyl or (1-4C)alkoxy substituent; or a non-toxic salt thereof.

8. A compound as claimed in claim 1 or 3 wherein R^3 is phenyl(1-4C)alkyl optionally bearing one or two substituents independently selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, cyano, trifluoromethyl, nitro, hydroxy, carboxy, (1-4C)alkanoylamino, (1-4C)alkanoyl, fluoro(1-4C)alkoxy, hydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, carbamoyl, alkyl or dialkylcarbamoyl of up to 7 carbon atoms, sulphamoyl, alkyl or dialkylsulphamoyl of up to 6 carbon atoms, (1-4C)alkoxycarbonyl, (1-4C)alkanesulphonamido, (1-4C)alkyl.$S(O)_n$- [in which n is zero, 1 or 2], 1H-tetrazol-5-yl, phenyl, phenoxy, benzyloxy, benzyloxycarbonyl, benzamido and benzenesulphonamido, the benzene moiety of the last six groups optionally bearing a halogeno, (1-4C)alkyl or (1-4C)alkoxy substituent; or a non-toxic salt thereof.

9. A compound of the formula I selected from:-

2,6-dimethyl-4-[N-(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]-pyrimidine;

2-ethyl-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)amino]-5,6,7,8-tetrahydroquinazoline;

2,6-dimethyl-5-iodo-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)-amino]pyrimidine;

2,6-diethyl-5-iodo-4-[(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)-amino]pyrimidine;

2,4-diethyl-8-[(2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl)]-pyrido[2,3-d]pyrimidin-7(8H)-one;

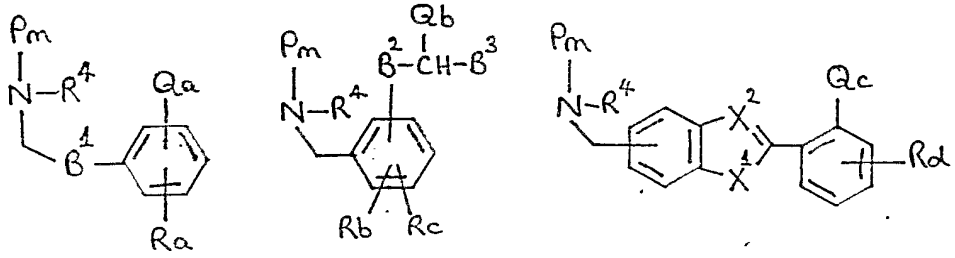
2,4-diethyl-8-[(2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]-5,6,7,8-tetrahydropyrido[2,3-d]pyrimidin-7-one;

2,6-diethyl-5-(4-methylphenyl)-4-[(2′-(1H-tetrazol-5-yl)methylamino]-pyrimidine; and
2,6-diethyl-5-(phenylmethyl)-4-[(2′-(1H-tetrazol-5-yl)methylamino]-pyrimidine; and the non-toxic salts thereof.

10. A salt as claimed in any one preceding claim which is selected from salts with acids forming physiologically acceptable anions and, for those compounds of the formula I which are acidic, alkali metal, alkaline earth metal, aluminium and ammonium salts, and salts with organic bases affording physiologically acceptable cations.

11. A process for the manufacture of a compound of the formula I, or a non-toxic salt thereof, as claimed in any preceding claim, which is characterised in that:-

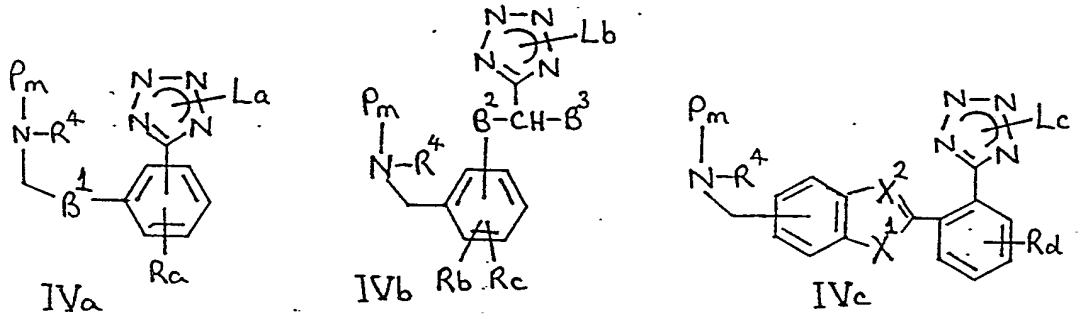
(a) For those compounds of formula I in which A^1 is a group of the partial formula IIa, IIb or IIc in which Za, Zb and Zc respectively are carboxy, a carboxylic acid derivative of the formula IIIa, IIIb or IIIc



IIIa IIIb IIIc

in which Qa, Qb and Qc respectively are protected carboxy groups selected from (1-6C)alkoxycarbonyl, phenoxycarbonyl, benzyloxycarbonyl and carbamoyl, is converted to carboxy;

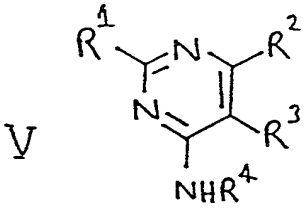
(b) For those compounds of formula I in which A^1 is a group of the partial formula IIa, IIb or IIc in which Za, Zb and Zc respectively are tetrazolyl, a compound of the formula IVa, IVb or IVc



IVa IVb IVc

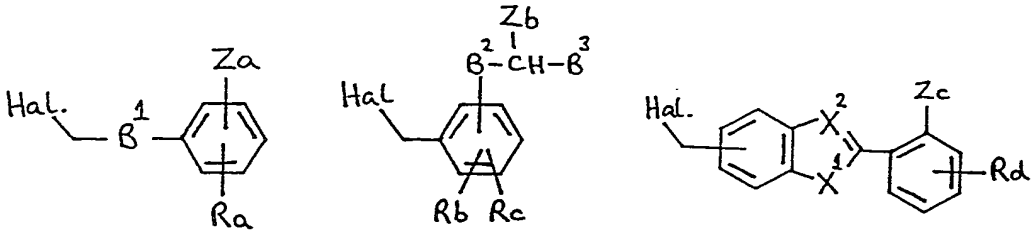
in which La, Lb and Lc respectively are protecting groups affixed to a nitrogen of the tetrazolyl moiety, is deprotected;

(c) An aminopyrimidine of the formula V



V

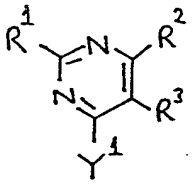
is alkylated with a compound of the formula VIIa, VIIb or VIIc



VIIa VIIb VIIc

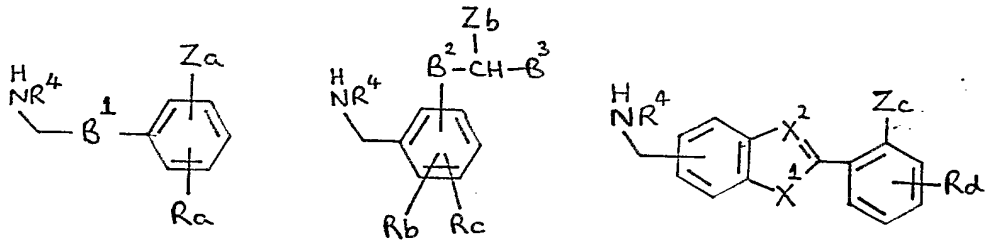
wherein Hal. stands for a suitable leaving group;

(d) A heterocyclic derivative of the formula VI



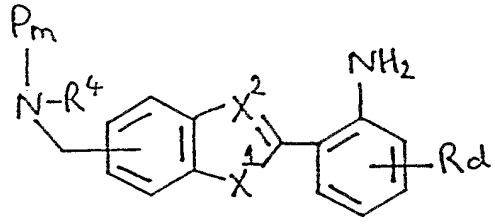
VI

wherein Y^1 is a suitable leaving group is reacted with an amine of the formula XIIIa, XIIIb or XIIIc



XIIIa XIIIb XIIIc

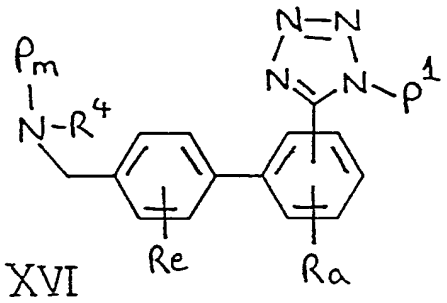
(e) For those compounds of formula I wherein A^1 is a group of partial formula IIc in which Zc is a group of the formula CF_3SO_2NH-, a compound of formula XIV



XIV

is reacted with trifluoromethanesulphonic acid anhydride; or

(f) For those compounds of the formula I wherein A^1 is a group of partial structure IIa in which Za is tetrazolyl, B^1 is p-phenylene optionally bearing a substituent selected from (1-4C)alkyl, (1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano and nitro, a compound of the formula XVI



XVI

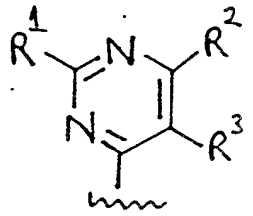
wherein P^1 is an electron-deficient phenyl group or a pyrimidyl or pyridyl group; Re is hydrogen, (1-4C)alkyl, (1-4C)alkoxy, halogeno, (1-4C)alkanoyl, trifluoromethyl, cyano or nitro, is reacted with a base selected from an alkali metal hydroxide, (1-12C)alkanolate, (1-12C)alkanethiolate, phenolate, thiophenolate or diphenylphosphide, wherein any phenyl ring of the latter three groups may optionally bear a (1-4C)alkyl, (1-4C)alkoxy or halogeno group;

whereafter: when a compound of the formula I is required wherein Za, Zb or Zc is -CO.NH.(1H-tetrazol-5-yl), a group of the formula $-CO.NH.SO_2R^8$ or an ester group, a carboxylic acid of the formula I in which Za, Zb and Zc is carboxy (or a reactive derivative of said acid) is reacted with 5-aminotetrazole, a sulphonamide of the formula $NH_2.SO_2R^8$ or a salt thereof or an appropriate alcohol or with a salt thereof;
when a non-toxic salt of a compound of formula I is required, it is obtained by reaction with the appropriate base affording a physiologically acceptable cation, or with the appropriate acid affording a physiologically acceptable anion, or by any other conventional salt formation procedure; and
when an optically active form of a compound of formula I is required, one of the aforesaid processes (a)-(e) is carried out using an optically active starting material, or

the racemic form of a compound of formula I in which Za, Zb or Zc is an acidic group is resolved by reaction with an optically active form of a suitable organic base, followed by conventional separation of the diastereoisomeric mixture of salts thus obtained, and liberation of

the required optically active form of said compound of the formula I by conventional treatment with acid;

and wherein the group Pm is a group of the partial formula



and wherein the generic radicals have any of the meanings defined in any of claims 1 to 8 unless otherwise stated.

12. A pharmaceutical composition which comprises a compound of the formula I, or a non-toxic salt thereof, as claimed in any of claims 1 to 10, together with a pharmaceutically acceptable diluent or carrier.

Patents Act 1977
Examiner's report to the Comptroller under Section 17 (The Search Report)

Application number
GB9225283.2

Relevant Technical fields

(i) UK Cl (Edition L) C2C CNF CTR CNG CZD

(ii) Int Cl (Edition 5) C07D

Search Examiner
D S LUCAS

Databases (see over)

(i) UK Patent Office

(ii) ONLINE DATABASE: CAS ONLINE

Date of Search
21 JANUARY 1993

Documents considered relevant following a search in respect of claims 1-12

Category (see over)	Identity of document and relevant passages	Relevant to claim(s)
P	EP 0475206 A2 ABBOTT (see Claim 3 and example 92)	1-12
P	US 5149699 A AMERICAN HOME PRODUCTS (see Claim 1, column 4 and the examples)	1-3 and 9-12

Category	Identity of document and relevant passages -61-	Relevant to claim(s)

Categories of documents

X: Document indicating lack of novelty or of inventive step.

Y: Document indicating lack of inventive step if combined with one or more other documents of the same category.

A: Document indicating technological background and/or state of the art.

P: Document published on or after the declared priority date but before the filing date of the present application.

E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

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Databases: The UK Patent Office database comprises classified collections of GB, EP, WO and US patent specifications as outlined periodically in the Official Journal (Patents). The on-line databases considered for search are also listed periodically in the Official Journal (Patents).

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